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EFFECT OF GLUTAMIC ACID ON MENTAL FUNCTIONING IN CHILDREN AND IN ADOLESCENTS

FREDERICK T. ZIMMERMAN, M.D.

BESSIE B. BURGEMEISTER, Ph.D.
AND
TRACY J. PUTNAM, M.D.
NEW YORK

THE PRESENT experiment is designed to investigate the effect of *l* (+)-glutamic acid on mental functioning in human subjects and is an outgrowth of a recent study by Zimmerman and Ross [1] on the effect of glutamic acid on maze learning in the white rat. In that experiment 200 mg. of glutamic acid was added to the diet of normal white rats for two weeks and its administration continued during the period of training. It was found that the glutamic acid group learned a simple maze much faster than the control group. In fact, the total number of trials required to learn was less than half that taken by the controls. The results were statistically significant in terms of time and accuracy scores, as well as in number of trials required to master the maze. The enhancement of learning was sufficiently striking to warrant an experimental investigation in the clinical field, especially since Price, Waelsch and Putnam,[2] in reporting on the incidence of petit mal and psychomotor seizures, observed a "universally increased mental and physical alertness" in the patients treated with glutamic acid and noted that the "degree of improvement in mental efficiency could not be correlated with the incidence of seizures."

The above mentioned experiments on the simple maze also suggested to Albert and Warden [3] the possibility that adding *l* (+)-glutamic acid

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From the Department of Neurology, Columbia University College of Physicians and Surgeons, and the Department of Psychology, Neurological Institute of New York.

1. Zimmerman, F. T., and Ross, S.: Effect of Glutamic Acid and Other Amino Acids on Maze Learning in the White Rat, Arch. Neurol. & Psychiat. **51:** 446-451 (May) 1944.

2. Price, J. C.; Waelsch, H., and Putnam, T. J.: *dl*-Glutamic Acid Hydrochloride in the Treatment of Petit Mal and Psychomotor Seizures, J. A. M. A. **122:**1153-1156 (Aug. 21) 1943.

3. Albert, K. E., and Warden, C. J.: The Level of Performance in the White Rat, Science **100:**476 (Nov. 24) 1944.

to the normal diet might enable white rats to learn more complex problems as well. These investigators, using a problem box,[4] found that supplementing the normal diet with *l* (+)-glutamic acid did cause white rats to advance further in a series of increasingly difficult problems.

MATERIALS AND METHODS

Choice of Patients.—The patients in this study form only a fractional part of the larger experiment now in progress, but results so far obtained seem to justify a preliminary report. The larger group includes children and adolescents who are mentally retarded or have convulsive disorders. The patients were selected by both neurologic and psychologic criteria. Neurologically they were selected so as to avoid, as nearly as possible, complicating organic features. This, however, could not be done in every instance, especially in the group with convulsive disorders. Psychologically, they were selected so as to obtain the effect of glutamic acid on mental ability in all age groups from childhood to adolescence at various intellectual levels. Seven of the 9 subjects completing the experiment are patients with convulsive disorders. Two are mentally retarded without convulsions.

The control group was selected primarily to ascertain the effect of control of seizures for varying periods of time on intelligence. Experiments on 9 subjects have been completed.

Dosage.—After neurologic examination and appropriate laboratory studies, an initial psychometric test was performed. Glutamic acid was then administered in gradually increasing doses. The dose was increased to the point where increased motor activity was apparent. This dosage was then maintained or reduced, depending on the degree of motor activity evoked. The criterion of increased motor activity was used, since this effect on rats was uniformly observed in the maze experiment.

Since much of the acid is lost by metabolism in the liver, by transamination and by competition of the various organs of the body for this essential amino acid, the effective dose must be determined empirically for each individual patient. The dose may range from 6 to 24 Gm. per day, but on the average 12 Gm. is sufficient. It is administered orally in tablet, powder or capsule form. Gastric distress is occasionally observed, but this can usually be obviated by discontinuing treatment for a few days and then beginning with smaller doses, which are gradually increased as tolerance develops. Table 1 shows the amount of glutamic acid given to each patient in the experimental group, as well as the data on reduction of seizures.

Methods of Testing.—The patients were tested at the beginning and end of a six month period in which they received glutamic acid therapy. They ranged in age from 16 months to 17.5 years, so that different measuring instruments were required for different age levels, as well as separate treatment of data. Prior to glutamic acid therapy, 6 of the group were given the Stanford-Binet intelligence test, form L, 1937 revision[5]; 1 was tested with the Wechsler-Bellevue scale[6];

4. Warden, C. J.; Jenkins, T. N., and Warner, L. H.: Comparative Psychology, New York, The Ronald Press Co., 1935, vol. 1, pp. 350-354.

5. Terman, L. M., and Merrill, M. A.: Measuring Intelligence, New York, Houghton Mifflin Company, 1937, p. 461.

6. Wechsler, D.: The Measurement of Adult Intelligence, Baltimore, Williams & Wilkins Company, 1939.

2 were given the Kuhlmann-Binet test [7]; 5, performance tests (Arthur point scale [8] or the Merrill-Palmer test [9]), and 7, the Rorschach ink blot test.[10] Retests with the same battery were made after the six month interval.

RESULTS OF TESTS

Table 2 shows the results of the Stanford-Binet test.

TABLE 1.—*Data on Medication and Reduction of Seizures in the Experimental Group*

Case No.	Diagnosis	Duration of Disorder on 1st Test	Number of Seizures: Before Medication	Number of Seizures: Reduced to	Medication
1	Idiopathic petit mal	8 yr.	1 per day	None	Phenobarbital, 0.06 Gm. t. i. d.; glutamic acid, 2 Gm., increased to 4 Gm. t. i. d.
2	Idiopathic petit mal	2 yr.	7-9 daily	1-2 daily	Glutamic acid, 4 Gm. t. i. d.
3	Idiopathic grand and petit mal	3½ yr.	Petit mal 10-14 per week; grand mal 1-2 per week	None	Diphenylhydantoin, 0.1 Gm. (per day, changed to methylphenylethylhydantoin, 0.1 Gm. q. i. d. glutamic acid 4 Gm. t. i. d.
4	Nonconvulsive disorder—mental retardation				Glutamic acid, 2 Gm. t. i. d.; increased to 4 Gm. t. i. d.; then reduced to 3 Gm. t. i. d.
5	Idiopathic grand mal	9 yr.	1 every 3-4 mo.	Same frequency, less severe	Diphenylhydantoin, 0.1 Gm. b. i. d.; phenobarbital, 0.06 Gm. t. i. d.; glutamic acid 4 Gm., increased to 6 Gm. t. i. d.
6	Idiopathic grand and petit mal	6 yr.	1 per day	None	Diphenylhydantoin, 0.1 Gm. b. i. d.; phenobarbital, 0.06 Gm. b. i. d.; glutamic acid, 2 Gm., increased to 8 Gm., t. i. d.
7	Idiopathic grand mal	4 yr.	1 per mo. for 1 yr.; free past 3 yr.	None	Diphenylhydantoin, 0.1 Gm. t. i. d.; phenobarbital, 0.03 Gm. t. i. d.; glutamic acid, 2 Gm., increased to 4 Gm. t. i. d.
8	Nonconvulsive disorder—mental retardation				Glutamic acid, 2 Gm., reduced to 1 Gm., increased to 4 Gm. t. i. d.
9	Idiopathic grand mal	10 mo.	From 10-14 daily to 1 per day	None	Phenobarbital 0.03 Gm. o. d.; glutamic acid, 2.5 Gm. t. i. d.

One subject (case 7), aged 16 years 5 months at the time of the first test, was tested with the Weschsler-Bellevue scale,[6] and the results appear in table 3.

7. Kuhlmann, F.: A Handbook of Mental Tests, Baltimore, Warwick & York, Inc., 1922.

8. Arthur, G.: A Point Scale of Performance Tests, New York, The Commonwealth Fund, 1930.

9. Stutsman, R.: Mental Measurement of Preschool Children, Yonkers-on-Hudson, World Book Company, 1931.

10. Rorschach, H.: Psychodiagnostik, Berne, E. Bircher, 1921.

Results of the performance tests are given in table 4.

Rorschach records were obtained from 7 of our 9 subjects before and after treatment with glutamic acid, and the results revealed increased productivity following the six month interval in all cases. Technical

TABLE 2.—*Ages and Scores on Stanford-Binet Intelligence Test of Experimental Group*

Case No.	Age at First Test	Intelligence Quotient	
		First Test	Retest
1	10 yr. 2 mo.	131	138
2	4 yr. 5 mo.	115	127
3	5 yr. 1 mo.	67	72
4*	17 yr. 7 mo.	57	64
5	13 yr. 8 mo.	47	56
6	12 yr. 10 mo.	45	54

* The patient had a nonconvulsive disorder.

TABLE 3.—*Results of the Wechsler-Bellevue Test*

	Initial Test	Retest
Full scale quotient	107 (average)	120 (superior)
Verbal quotient	106	116
Performance quotient	105	119
Subtests		
Information	11	11
Comprehension	11	11
Arithmetic	12	17
Digits	9	9
Similarities	8	11
Vocabulary	13	13
Picture completion	10	10
Picture arrangement	12	17
Object assembly	9	11
Block designs	10	13
Digit-symbols	13	14

TABLE 4.—*Changes in Mental Age on Performance Tests in Experimental Group*

Case No.	Test	Mental Age, First Test	Mental Age, Retest After 6 Mo.
1	Arthur	10 yr. 11 mo.	15 yr. 8 mo.
2	Merrill-Palmer	4 yr. 3 mo.	6 yr. 4 mo.
3	Merrill-Palmer	3 yr. 1 mo.	3 yr. 11 mo.
4	Arthur	7 yr. 0 mo.	8 yr. 10 mo.
5	Merrill-Palmer	3 yr. 11 mo.	4 yr. 7 mo.

difficulties of interpretation prohibit our including a detailed analysis of the records in this paper; this will be dealt with in a report on the large experiment now in progress. It seems worth while, however, to include a sample record (case 3) here, in order to illustrate that the

retest records were characteristically more dynamic than the initial records and suggested basic changes in the personality structure.

Rorschach Record 1 Initial Test Intelligence quotient 67 Age 5 yr. 1 mo.			Rorschach Record 2 Retest Intelligence quotient 72 Age 5 yr. 7 mo.		
Card No.	Seconds Before Response	Response	Card No.	Seconds Before Response	Response
I	4	A boat	I	7	Two men
II	2	A boat	II	5	A tree—no—I have a Christmas tree—two red firemen (inquiry)—here is the driver (points to right side)—and here's the fellow that rides on the back (points to the left side)
III	2	A boat	III	8	I don't know. Two little ducks swimming
IV	1	A boat	IV	17	I don't know. A tail—a pussy cat's tail
V	1	A boat	V	12	I don't know. An Indian
VI	3	A boat	VI	6	A cross
VII	2	A boat	VII	17	I don't know. Two little Indians fighting
VIII	1	A boat	VIII	5	A Christmas tree
IX	3	A boat	IX	6	Two little Indians
X	2	A boat	X	3	A Christmas tree

In cases 8 and 9 the Kuhlmann-Binet test [7] was required because of serious retardation.

CASE 8.—The chronologic age at the time of the first test was 2 years. A basal mental age of 3 months was established, all tests for the six month level being creditable except for reaction to source of sound. In tests at the 1 year level sitting unsupported and imitation of movement constituted the child's highest successes. As scored, her performance rated 8 months.

A retest after a six month period revealed a basal mental age of 6 months. No credit for speech was possible, although she then had a better understanding of words. A striking improvement in the motor field was seen in her ability to walk with help and to lower herself from a standing to a sitting position, although she did the latter in an awkward manner. Her highest successes now consisted in cooperation in dressing, as she held out her arm when attempts were made to put on her coat, recognized objects and spit out solids, according to report. As scored, her performance on the retest rated 14.4 months, which is a gain in mental age of slightly more than 6 months in a six month interval, a normal rate of development.

CASE 9.—Chronologic age at the time of the first test was 16 months. On the Kuhlmann-Binet material, carrying the hand or object to the mouth, reacting to sudden sounds and binocular coordination were creditable at the 3 month level. The child's highest questionable reaction was to source of sound at the 6 month level. His total performance measured just short of the 3 month level.

Retests six months later showed creditable results in all tests at the 3 month level. In tests at the 6 month level, balance, source of sound and use of the opposing thumb earned credit. The most noticeable feature was the child's ability to walk alone and to sit alone. These earned credit at the 1 year level. According to report, he was also said to spit out solids, a performance giving him credit at the 18 month level. His total performance now rated 7.2 months and represented a gain in mental age of more than 4 months in an interval of six months.

EFFECT OF CONTROL OF SEIZURES ON INTELLIGENCE

Seven of the 9 subjects completing the experiment are patients with convulsive disorders, and 2 are mentally retarded without convulsions. Such a sample, consisting almost entirely of patients with convulsive disorders, presents a special problem in estimating the effect of glutamic acid on mental functioning, since it raises the question whether control or reduction of seizures may result in an increase in psychologic test scores.

Several statistical studies which have appeared fail to demonstrate a positive relationship between reduction in number or severity of seizures with anticonvulsive medication and increase in intelligence quotient on the Stanford-Binet test. Much of the work done has concerned itself with the problem of mental deterioration and its arrest under drug therapy. Dawson and Conn,[11] Kugelmass, Poull, and Rudnick,[12] and others reported that children showed a decrease in intelligence quotient scores if medication failed to decrease the number and severity of seizures but did not establish the fact that reduction or control resulted directly in an increase of scores.

Yacorzynski and Arieff,[13] in studying 63 patients with "nonorganic epilepsy," subjected 49 to bromide therapy over a period of six months to five years, gave 9 phenobarbital from one to four years and kept 5 without medication. Fourteen of the patients were under 16 years of age. All patients were given the Stanford-Binet test two to four times during an interval of one to seven years. The authors concluded that changes in individual scores are not associated with bromide treatment and that "there appears to be no relationship between the reduction in the number or severity of seizures and the changes of the intelligence quotients."

Similar findings were reported by Fetterman and Barnes [14] in their study of 46 adult patients under phenobarbital therapy who were retested with the Stanford-Binet scale after two years, the data suggesting that "the intelligence quotient is not materially altered by the continued use of sedative drugs." Collins [15] also concluded that phenobarbital has little effect on intelligence.

11. Dawson, S., and Conn, J. C. M.: The Intelligence of Epileptic Children, Arch. Dis. Childhood **1**:142-151, 1929.

12. Kugelmass, I. N.; Poull, L. E., and Rudnick, J.: Mental Growth of Epileptic Children, Am. J. Dis. Child. **55**:295-303 (Feb.) 1938.

13. Yacorzynski, G. K., and Arieff, A. J.: Absence of Deterioration in Patients with Nonorganic Epilepsy with Especial Reference to Bromide Therapy, J. Nerv. & Ment. Dis. **95**:687-697, 1942.

14. Fetterman, J., and Barnes, M. R.: Serial Studies of the Intelligence of Patients with Epilepsy, Arch. Neurol. & Psychiat. **32**:797-801 (Oct.) 1934.

15. Collins, A. J.: Psychometric Records of Institutionalized Epileptics, J. Psychol. **11**:359-370, 1941.

Ross and Jackson [16] reported on the effect of diphenylhydantoin given to a series of 73 patients, ranging in age from 11 to 51 years, 29 of whom had a disorder diagnosed as idiopathic epilepsy. These patients received 0.1 to 0.5 Gm. of diphenylhydantoin sodium daily over an interval of twelve to eighteen months and were tested and retested with the Stanford-Binet scale. In 65 per cent of the group seizures were reduced 75 per cent or more, and the authors stated:

> One might expect that with the heightening of interest, initiative, and alertness shown by many of the patients, their intelligence ratings would be raised. They actually give the impression of being more intelligent than at the beginning of treatment. However, this appearance is deceptive, for there obtained practically a balance between raised and lowered intelligence ratings in the face of equivalent seizure reduction.

Performance tests (the Arthur scale) were also given, and results were more striking.

> Performance ratings were raised appreciably in a small percentage of patients. The drug seemed to have a greater beneficial effect in this capacity than on intelligence.

Peoples and Tatum [17] found no significant change in the intelligence of 12 morons and idiots treated with diphenylhydantoin, but 5 showed gains in the motor field and improvement in general behavior.

It seems necessary to accept with reservations some of the evidence from the literature for groups which include adults because of the questionable validity of intelligence "quotients" so obtained with the use of the Stanford-Binet scale on adult groups. Since the Stanford-Binet scale assumes a linear relationship between chronologic age and mental age, which does not hold for adults, it appears wiser to substitute "score" for "intelligence quotient" in interpreting results of tests for adults. Nevertheless, the same lack of improvement in retest scores does seem to be indicated among adults as is found among children with convulsive seizures which are controlled or reduced by medication.

Control Group.—As a check on the findings of other investigators and on the results for the present experimental group, clinic children and adolescents are being studied who were tested before and after a period in which convulsive seizures were controlled or appreciably reduced by medicaments other than glutamic acid. To date, 9 such children have been studied, and data obtained from this control group are presented in table 5.

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16. Ross, A. T., and Jackson, V.: Dilantin Sodium: Its Influence on Conduct and on Psychometric Ratings of Institutionalized Epileptics, Ann. Int. Med. **14:** 770-773, 1940.

17. Peoples, S. A., and Tatum, A. F.: Dilantin Sodium Therapy in Deteriorated Epileptics Refractory to Other Treatment, J. M. A. Alabama **12:**197-199, 1943.

For 1 subject only was the intelligence quotient raised (1 point), whereas for 7 of the 9 subjects a decrease in score occurred, as is shown in table 6. Even though the control group is a small one, the data certainly do not suggest that an increase in the intelligence quotient

TABLE 5.—*Data on Reduction of Seizures in the Control Group*

Case No.	Diagnosis	Duration of Disorder on First Test	Number of Seizures: Before Medication	Number of Seizures: Reduced to	Medication
1	Idiopathic grand mal	3 mo.	1 per hr.	None for 5 mo.	Diphenylhydantoin, 0.06 Gm. t. i. d.
2	Idiopathic focal motor cortical seizures	7 yr.	2-6 per mo.	None for 1 yr.	Phenobarbital, 0.015 Gm. t. i. d.
3	Idiopathic grand mal	3 yr.	Series	None for 4 yr.	Phenobarbital, 0.03 Gm. b. i. d.; diphenylhydantoin, 0.03 Gm. per day
4	Idiopathic grand and petit mal *	6 yr.	1-3 grand mal daily; 10-200 petit mal daily	No grand mal for 1 yr.; petit mal, 1-2 daily	Phemitone, 2 Gm. q. i. d.
5	Idiopathic petit mal	5 mo.	10-15 daily	None for 11 mo.	Phenobarbital, 0.015 Gm. t. i. d.
6	Idiopathic petit mal	1 yr.	3-6 daily	None for 2 yr.	Diphenylhydantoin, 0.1 Gm. t. i. d.
7	Idiopathic grand and petit mal	5 yr.	4-7 grand mal daily; 10-15 petit mal daily	None for 3 yr.	Diphenylhydantoin, 0.1 Gm. t. i. d.; phenobarbital, 0.03 Gm. t. i. d.
8	Idiopathic grand mal	3 yr.	10-15 a mo.	None for 11 mo.	Phenobarbital, 0.1 Gm. per day
9	Idiopathic grand and petit mal	6 yr.	6 grand mal and petit mal daily	No grand mal for 3 yr.; no petit mal for 6 mo.	Diphenylhydantoin, 0.1 Gm. t. i. d.

* A severe organic condition is also present.

TABLE 6.—*Age and Intelligence Test Scores of Control Group*

Case No.	Age at First Test	Date: First Test	Date: Second Test	Intelligence Quotient: First Test	Intelligence Quotient: Second Test
1	8 yr. 0 mo.	October 1945	March 1946	110	110
2	5 yr. 5 mo.	December 1936	May 1941	102	99
3	6 yr. 3 mo.	September 1941	March 1946	93	90
4	7 yr. 4 mo.	October 1942	May 1943	93	72
5	6 yr. 11 mo.	June 1943	March 1946	90	74
6	7 yr. 11 mo.	October 1943	February 1946	86	76
7	12 yr. 0 mo.	January 1943	October 1943	71	64
8	9 yr. 0 mo.	November 1944	March 1946	70	71
9	8 yr. 11 mo.	March 1942	January 1946	56	53

accompanies reduction of seizures. Our results, therefore, agree substantially with others reported in the literature.

Evaluation of Experimental Results.—The results given in table 2 are in striking contrast to those obtained for the control group (table 6), since in every instance a definite increase in the retest intelligence quotient appears in the experimental group. Some of the change may be accounted for in terms of practice effect, although it is believed that this

is negligible, and some in terms of variability in retest scores. Variability, however, is just as likely to produce a lowering in the individual retest score as it is to result in a higher quotient. Ross and Jackson [16] pointed out that a gain of 10 points or more in the retest quotient of 6 of their 73 patients was offset by a loss of 10 points or more in the quotient of 4 other patients. Because chance fluctuations tend to balance each other in this way, little change in the average intelligence quotient for a group is to be expected from chance factors. For all their 63 patients, Yacorzynski and Arieff [13] obtained an average shift in the intelligence quotient of only 1.3 points, which is not significant. Their findings are similar to those of other investigators, showing only small differences in retest scores and do not reveal a consistent trend in a positive direction, as do our retest intelligence quotients.

TABLE 7.—*Dispersion of Retest Scores on the Stanford-Binet Test* *

Intelligence Quotient	Probable Error of Intelligence Quotient, Points	Four Times Probable Error of Intelligence Quotient, Points
130 and over	3.54	14.16
110 - 129	3.29	13.16
90 - 109	3.04	12.16
70 - 89	2.60	10.40
Below 70	1.49	5.96

* After Terman and Merrill.[5]

TABLE 8.—*Changes in Intelligence Test Scores of the Experimental Group Given the Stanford-Binet Test*

Case No.	First Intelligence Quotient (Average 77)	Retest Intelligence Quotient (Average 85)	Point Change + −	Chances of a Significant Difference
1	131	138	7	80 in 100
2	115	127	12	98 in 100
3	67	72	5	97 in 100
4*	57	64	7	100 in 100
5	47	56	9	100 in 100
6	45	54	9	100 in 100

* This patient had a nonconvulsive disorder.

In evaluating test reliability, level of intelligence is a potent factor. Terman and Merrill [5] have shown that the dispersion of retest scores on the Stanford-Binet test increases with the higher intelligence quotients, as shown in table 7. This means there is practical certainty that a variation of 14.16 points or more would not occur by chance for a subject with an intelligence quotient of 130 or more, or one of 5.96 points or more for a subject with an intelligence quotient of 70 or below.

Analysis of our data according to the Terman and Merrill criteria is presented in table 8.

It may readily be seen from table 8 that for the group our data yield an average increase of 8 points in intelligence quotients on retest, with no negative deviations whatsoever. Of special importance is the fact that for the subjects with the three lowest initial scores, one of whom has a nonconvulsive disorder, statistically significant differences in retest quotients are indicated. Higher quotients would least be expected for persons with this degree of retardation, since under ordinary conditions the discrepancy between chronologic and mental age tends to grow wider as chronologic age increases and more often results in a lowering of the intelligence quotient.

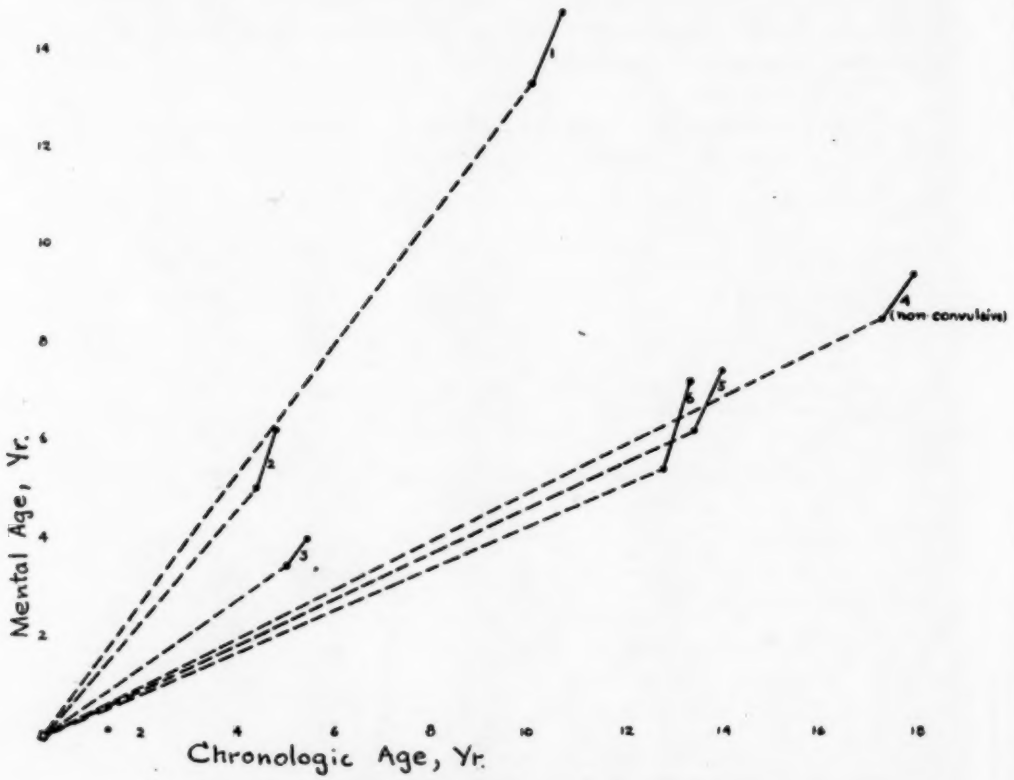

Fig. 1.—Relation of mental age to chronologic age before and during glutamic acid therapy for 5 patients with convulsive disorders and 1 patient with a nonconvulsive disorder as shown by verbal test scores. The previous rate of development is shown by the broken line; the rate during therapy, by the solid line.

Impressive as are these changes in intelligence scores, their significance becomes even clearer when they are viewed as ratios of mental age to chronologic age (fig. 1).

For all subjects, sharp, positive increments in mental ages are apparent after treatment with glutamic acid with the mental ages of the

low grade subjects increasing at a rate faster than is expected in children of average intelligence (fig. 2).

Table 6 shows a positive change of 13 points in the full scale Wechsler-Bellevue quotient, with some gains on both verbal and performance sections, results being consistent with those obtained on the Stanford-Binet tests. Consistent increases in individual performance scores are apparent, without negative deviations, as they are on the verbal intelligence test material. Some gains would, of course, be expected, because the group is older on retest. If, however, the scores are considered

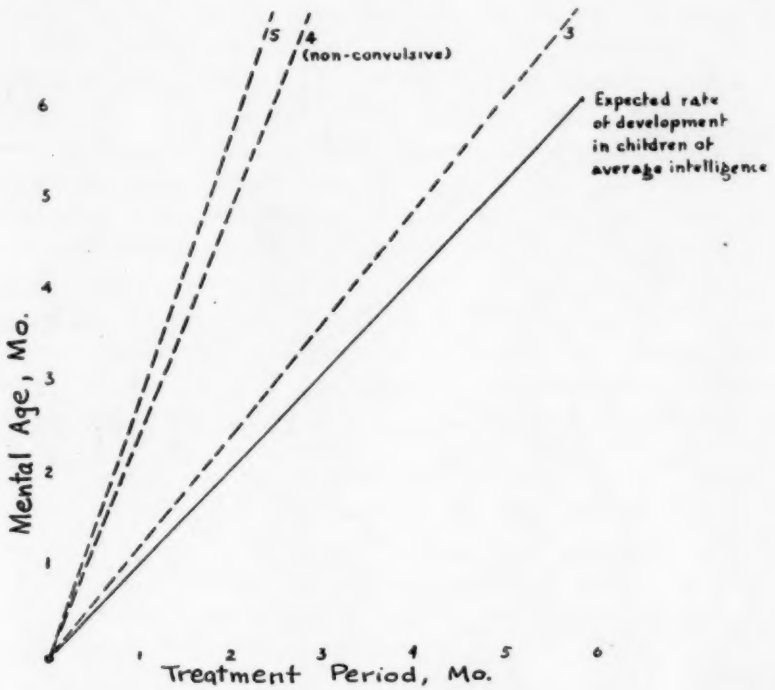

Fig. 2.—Increment in mental age during glutamic acid therapy in 3 mentally retarded children, 2 of whom had convulsive disorders, as shown by verbal test scores. Subject *3* made a gain in mental age of 7 months; subject *4*, a gain of 14 months, and subject *5*, a gain of 16 months, in a six month experimental period. The expected rate of development (shown by the solid line) in children of average intelligence is 6 months in a six month period.

in connection with chronologic age (fig. 3), more than the normally expected rate of increase is maintained, and more than in the case of the verbal intelligence test material.

In the control group, however, a slight gain in retest performance scores is also indicated, and it is believed that in both groups reduction of seizures may account for some of the improvement found on motor tests.

As shown in the first Rorschach record in the case cited, little relationship exists between concept and blot for any of the cards, responses being typical of very young children, who frequently show perseveration on an idea which seems acceptable to them. In contrast to this, the responses of the second record are of very good form quality and without exception fit the contour of the blot material. While the retest records of all subjects in our experimental group do not show such striking improvement as does that in the case cited, each is definitely more productive. This suggests that glutamic acid has an effect on mental func-

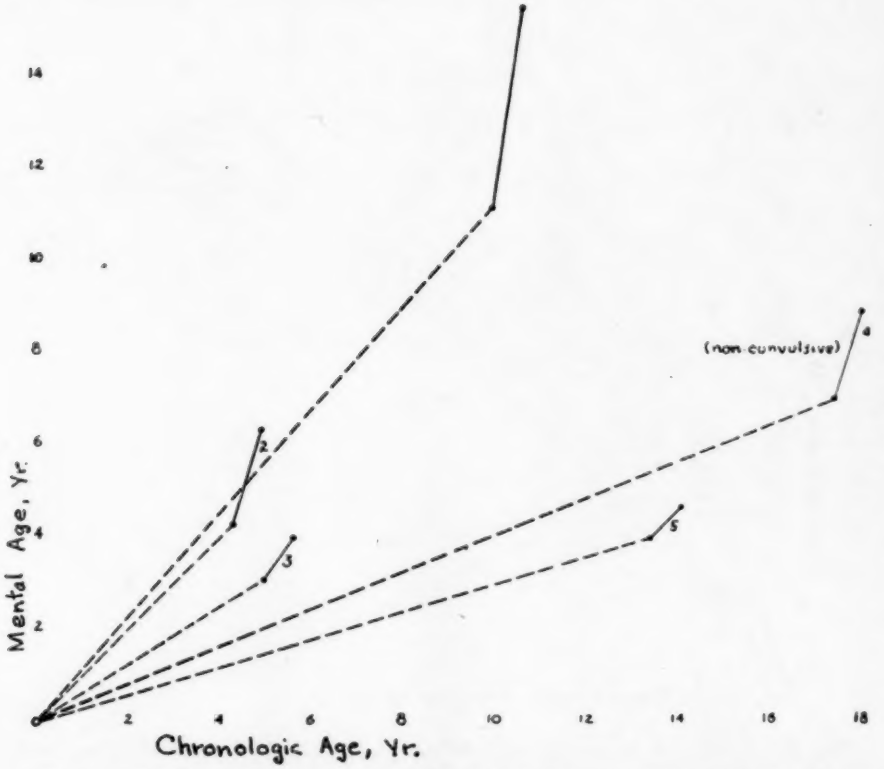

Fig. 3.—Relation of mental age to chronologic age, expressed in years, before and during glutamic acid therapy for 4 patients with convulsive disorders and 1 patient with a nonconvulsive disorder, as shown by performance test scores. The previous rate of development is shown by the broken line; the rate during glutamic acid therapy, by the solid line.

tioning, which not only is reflected in verbal and performance test scores but can be observed in rather basic personality changes, under the conditions of our experiment.

In cases 8 and 9 progress was much more rapid than would have been anticipated from the development prior to the glutamic acid therapy, results which are consistent with those for the rest of the experimental group.

COMMENT

On verbal, motor and personality tests given, definite improvement following glutamic acid therapy could be observed in each of our 9 subjects during a six month interval. A number of experiments have pointed to the fact that *l* (+)-glutamic acid has a particular relation to cerebral metabolism. Weil-Malherbe [18] reported that *l* (+)-glutamic acid is the only amino acid known to be metabolized by slices of brain tissue. Recent investigations of Nachmansohn and his associates [19] suggest that the release of acetylcholine is intrinsically connected with the electrical changes during nerve activity. They found that the energy of the action potential is derived from energy-rich phosphate compounds and concluded that these compounds yield the energy for the formation of acetylcholine. As a result of these observations, they isolated an enzyme from the brain which synthesizes acetylcholine.[20] This enzyme, choline acetylase, becomes inactive on dialysis. Addition of *l* (+)-glutamic acid reactivates the enzyme.[21]

While the precise mechanism of the action of glutamic acid on the rate of acetylcholine has still to be elucidated, the intrinsic connection of an acetylcholine with nerve activity and the demonstration of an increased rate of formation of acetylcholine in the presence of glutamic acid in vitro make it possible to assume that the physiologic basis of the observed effects of glutamic acid is in some way related to the formation of acetylcholine. At present this seems to be the best interpretation.

SUMMARY

The results here reported must be considered tentative because of the smallness of the group, but the consistent improvement reflected in the psychologic test scores under the conditions of our experiment suggests that glutamic acid may have a genuine facilitating effect on mental functioning in human subjects, as it does on maze learning in the white rat.

APPENDIX

While the study is primarily objective, clinical observations in the main support the quantitative findings, and a clinical abstract of each case is accordingly appended.

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18. Weil-Malherbe, H.: Studies on Brain Metabolism: Mechanism of Glutamic Acid in Brain, Biochem. J. **30**:665-676, 1936.

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CASE 1.—A boy 10 years old had a history of petit mal attacks occurring on the average of one a day since the age of 2 years. The general physical and neurologic status was normal. A roentgenogram of the skull revealed nothing abnormal. The electroencephalogram showed wave and spike formations and flat-topped slow activity dominating the pattern in all leads. The petit mal attacks were completely controlled with phenobarbital, 0.06 Gm. given three times a day. After a psychometric examination he was given *l* (+)-glutamic acid, 2 Gm. three times a day. No change in behavior was noted. When the dose was increased to 4 Gm. three times a day, the mother reported that he was very restless and overactive. His teacher reported poor conduct in school, which seemed to be due to greater distractibility. He continued to be free of seizures as long as he remained under treatment with phenobarbital and glutamic acid.

The behavior of this patient can possibly be explained on the basis of lack of need of such large doses of glutamic acid, since his intelligence quotient was high in the first place.

CASE 2.—A boy 4 years old had been having attacks of petit mal for two years. There was a history of a head injury without loss of consciousness six weeks before the onset of the spells. The physical and neurologic status was normal. A roentgenogram of the skull and an electroencephalogram were normal. Treatment with diphenylhydantoin sodium and phenobarbital was ineffective. After a psychometric examination treatment with *l* (+)-glutamic acid (3 Gm. daily) was substituted. The number of seizures dropped from seven or nine to one or two per day. The dose increased to 6 Gm. per day, after which the mother reported that the child was much more alert and active. When the dose was gradually increased to 24 Gm. per day, the child became very restless and overactive and was unable to sleep at night. A subsequent dose of 12 Gm. per day maintained an optimum degree of activity and alertness. He continued to have one to two seizures per day.

CASE 3.—A boy aged 5 years had been having attacks of disordered consciousness since the age of 16 months, beginning as petit mal and subsequently complicated with grand mal attacks. Several physical and neurologic examinations showed nothing abnormal. A roentgenogram of the skull revealed a disproportionately small cranial cavity, consistent with microcephaly. After a psychometric examination the boy was given 4 Gm. of *l* (+)-glutamic acid three times a day in addition to 0.1 Gm. of diphenylhydantoin sodium daily, which he had been receiving previously. The number of grand mal seizures was not affected, but the petit mal attacks dropped from ten or fourteen per week to four or seven per week. The mother reported that the child was much more tractable. Whereas previously he fought with the other children a great deal, he was now much more sociable and played with the other children nicely. The change in behavior began to be apparent about two weeks after the start of the glutamic acid therapy.

The father, who had not seen the child for seven weeks and was unaware of the treatment, spontaneously remarked that he appeared much brighter and more alert.

When seen in the clinic, the child showed increased motor activity. While previously he had sat quietly in his chair, he now was inquisitive and moved around frequently. Two months later the family reported considerable improvement in memory. He began to talk about the radio, which had been repaired over a year before. He also began to remember the names of people; when

taken with his mother shopping, he remembered the various groceries she bought in different stores. He also began to recognize colors. He continued this improvement throughout the six month testing period.

After a toxic reaction to an increased dose of diphenylhydantoin, treatment was changed to administration of methylethylphenylhydantoin, 0.1 Gm. four times a day. This drug, in conjunction with 12 Gm. of glutamic acid, controlled both types of seizures completely.

CASE 4.—A girl aged 17 years, who appeared much younger than her chronologic age, gave a history of normal birth. She walked at 15 months, said words at 2 years and used sentences between 2 and 3 years of age. Although at one time she tended to stay by herself, she later became more friendly, but she played with younger children and was always the oldest in her group. The situation was complicated by rejection on the part of the mother, who preferred an older, normal, daughter.

In the school which she attended for one year before coming to our attention, she was doing arithmetic at the fifth grade level and was reading at the seventh grade level. On the playground she took part in all group activities but needed to be encouraged to do so. In the dormitory she was slow but did everything for herself. She was careless about her appearance and person and had to be given assistance at the time of her menstrual periods. Occasionally she wet the bed or soiled herself, but this was apparently done in retaliation against a staff member whom she did not like. Her relations with other children eventually became very poor. She pinched, slapped and pushed them without any apparent provocation. She became increasingly withdrawn, and because of this the parents were advised to remove the child and seek psychiatric advice.

When first seen, she appeared dull and withdrawn, did not hold herself erect and walked with a careless slouch. She appeared untidy in her dress and person. She was obviously resentful toward her mother, who returned the sentiment in good measure. After a psychometric examination glutamic acid medication was started. She was first given 2 Gm. three times a day, and the dose was gradually increased to 4 Gm. three times a day. With the latter dose she became very overactive and more antagonistic toward her mother. The older sister, who was much more impersonal in her observations than the mother, said, however, that the patient seemed to "think more about herself." The dose was reduced to 3 Gm. three times a day, and she became more tractable, with evidence of more continued interest in things. When she was seen at the end of the six month experimental period, her facial expression was more alert, and her negativistic behavior was not so much in evidence, even in the presence of her mother. She stood more erect, and her exaggerated slouch had disappeared.

CASE 5.—A boy aged 13 years had been having attacks of grand mal since the age of 4 years. He first came to our attention at the age of 2 years, when a diagnosis of serious mental retardation was made. He was premature and was born by cesarian section. A cousin had convulsions for eighteen years. The general physical and neurologic status was normal. Roentgenograms of the skull revealed no abnormality. The pneumoencephalogram showed diffuse cerebral agenesis or atrophy and localized agenesis or atrophy in the anterior parietal region, with moderate general dilatation of the ventricular system. The electroencephalographic record was disorganized, with much low to medium activity everywhere, and was interpreted as definitely abnormal. The patient had one attack every three to four months, usually rather severe and lasting from forty-

five minutes to one and one-half hours. Diphenylhydantoin sodium, 0.1 Gm. twice a day, and phenobarbital, 0.03 Gm. three times a day, reduced the severity of the seizures but not the frequency. After a psychometric examination the patient was given 4 Gm. of *l* (+)-glutamic acid three times a day, in addition to the diphenylhydantoin and phenobarbital. About a month later his mother reported that he appeared to be more alert and attentive. The dose was then increased to 6 Gm. three times a day. Two months later his mother reported he was much more alert, was no longer shy and was making a much better social adjustment. She said, "Before, the children would never play with him because he was too slow in grasping things. Now they have accepted him, and he gets along fine with them. He used to be seclusive—never wanted to go out—now he is anxious to go out and play with the other children. He enters into the games and has a good time and is not shy any more. Even the neighbors notice it."

Three months later his mother reported that in addition to the improvement already noted he "picks up the newspaper and sounds out the words, trying to read."

During the six month experimental period the seizures were not controlled, although they were less severe. If anything, the frequency was increased to two or three attacks per month. No great effort was made to control the seizures in order to see what effect the glutamic acid would have on mental ability in the presence of seizures.

Case 6.—A boy aged 12 years had been having grand and petit mal attacks on the average of one a day since the age of 6 years. The general physical and neurologic status was normal. A roentgenogram of the skull revealed an unusually thick calvaria and conspicuous diploic structures but no signs of increased intracranial pressure or intracerebral calcification. The electroencephalographic record was quite abnormal, without alpha activity at any time. An irregular mixture of medium voltage, slow activity was continuously seen, with frequencies varying from 3 to 6 per second. In addition, many single "slow" spikes and atypical spike and wave groups were recorded from both occipital areas. The record was considered grossly abnormal with convulsive patterns.

The grand and petit mal seizures were controlled with diphenylhydantoin sodium, 0.1 Gm. twice a day, and phenobarbital, 0.03 Gm. twice a day, after which the patient was given a psychometric examination and 2 Gm. of *l* (+)-glutamic acid three times a day, in addition to the aforementioned medication. One month later, although the seizures were still controlled, there was no visible evidence of improved mental status. The amount of *l* (+)-glutamic acid given was then gradually increased to 8 Gm. three times a day. Two weeks after the inauguration of the latter dosage the patient appeared much more alert mentally, lost his indifferent manner and was genuinely interested in what went on about him. His facial expression was no longer dull, and he smiled appropriately.

One month later his mother said, "He used to get lost when I sent him on an errand and couldn't find the house. Now he finds it easily." She also reported, "He used to be very poor at riding a bicycle. Now he is very good. He used to be awkward and clumsy in handling eating utensils, such as a knife and fork, as though he didn't quite know how to use them. Now he handles them all right." She said further, "He used to be a little uncertain in his gait. Now I don't notice it any more. Then, too, he used to stutter a lot and fumble for words. This has disappeared. He was also 'hard-headed' and stubborn. Now he is much more

tractable. He hasn't been to school for three years and was in the fourth grade. Now they took him back to school and put him in 6 A. He certainly isn't nervous any more and 'catches on' a lot quicker."

CASE 7.—A girl aged 16 years had been having grand mal attacks since the age of 12 years, the seizures occurring on the average of once a month and lasting a few minutes. The general physical condition was normal. Neurologic examination revealed nothing abnormal except for congenital nystagmus. A roentgenogram of the skull was normal. Three electroencephalograms were taken at the ages of 12, 14 and 16 years, respectively. The patterns of all three were interpreted as consistent with a convulsive disorder, with a suggestion of a focus in the occipital area in the first two and a focus in the right parieto-occipital region in the third. A pneumoencephalogram was also normal. The patient had for three years been under treatment with diphenylhydantoin sodium, 0.1 Gm. three times a day, and phenobarbital, 0.03 Gm. three times a day, and had been free of seizures. After a psychometric examination she was placed under a regimen of *l* (+)-glutamic acid, 2 Gm. three times a day. One month later no change was noted. She still presented her characteristic picture of listlessness and indifference, with a certain constant querulous way of discussing her problems. From her facial expression she appeared apathetic and slightly anxious. The dose of glutamic acid was then increased to 4 Gm. three times a day, and when she was seen about five weeks later she was smiling and vivacious. Whereas previously she had complained about her teachers and her inability to get good grades, she now said she was getting good marks and was no longer bothered by the teacher, though she still thought she was a "pill." In later months she regained a normal interest in social activities and talked about her "dates," dancing and so forth. She has maintained this improvement to date with the same medication.

CASE 8.—A girl 2 years of age had a history of retarded development, first noted about the age of 6 months. Instrumentation was necessary at birth. She had her first teeth at 6 months of age and seemed unusually quiet. At 7 months she did not reach for things and did not try to sit up. She sat up at 15 months, but at 2 years of age she made no effort to walk or talk. She was bottle fed from birth, and at 23 months of age she was unable to hold her bottle. The family history was noncontributory. Physical examination showed defective musculature, with no evidence of abnormal control of muscular movements. The condition was believed to be that of a developmental defect of the muscular system, with defective cerebral development as well. Roentgenograms of the skull and spine revealed nothing abnormal. Chronaxia showed no evidence of disease or defect of the lower motor neurons.

After a psychologic examination the child was given glutamic acid, 2 Gm. three times a day. One month later the parents reported that the child was more alert and attempted to gain their attention. She was able to pile blocks one on the other, a performance of which she had not been capable before. Medication was then discontinued for a month because of a gastric disturbance, and the child lost interest in her blocks and was unable to pile them up. The medication was then started again, with a dose of 1 Gm. of glutamic acid three times a day, and the dosage was gradually increased until she was able to tolerate 4 Gm. three times a day. In the next two months she learned to pile up her blocks again and began to notice things. When seen just before the end of the six month experimental period, she had a bright expression and showed motor overactivity. She was able to pull herself up to a standing position and could walk with assistance.

The attention span had increased considerably. She reached for things, and when they were just out of her reach she persisted in trying to get them. The parents also reported she said the words "da-da" after them.

Case 9.—A boy 16 months of age had had a normal birth. The mother noticed that the baby, although gaining weight normally, never smiled, followed objects with his eyes or held objects in his hands. His head also appeared slightly larger than that of other infants. At the age of 6 months he began to have attacks characterized by flexion, stiffness and slight trembling of all four extremities. These attacks lasted about two minutes and were followed by sleep for a half-hour or more. They recurred from ten to fourteen times a day at first but later subsided to an average of one a day. The patient was never able to sit up, roll around in bed or stand up. Gain in weight and stature was apparently normal. Physical examination revealed slight enlargement of the head, which was thought to represent abortive hydrocephalus. The rest of the neurologic examination revealed no abnormalities. Roentgenograms of the skull and spine were normal. The seizures were controlled during the stay in the hospital with 0.03 Gm. of phenobarbital daily.

After a psychometric examination, glutamic acid therapy was started, the dose gradually being increased to 2.5 Gm. three times a day. Four weeks later the child was observed to be more active, turning over and getting up on his knees. Two months later he sat up without support, walked when held, was more playful and noticed things more. At the end of the six month experimental period he maintained his steady improvement and was walking alone.

710 West One Hundred and Sixty-Eighth Street.

NEUROLOGIC MECHANISM FOR CERTAIN PHENOMENA IN TETANY

ERIC KUGELBERG, M.D.
STOCKHOLM, SWEDEN

THIS PAPER is first and foremost a contribution to the elucidation of the neurologic mechanism for the Trousseau and von Bonsdorff phenomena, with special regard to the changes in excitability of the nerve during and after ischemia. In the second place, it is intended to throw further light on the mechanism for the spontaneously occurring symptoms of tetany.

The Trousseau phenomenon signifies here the tetanic spasm following pneumatic compression of the arm, while the von Bonsdorff phenomenon means the facilitation of tetanic spasm induced by hyperventilation after preceding compression of the arm. Closer analysis shows, however, that not only the spasm but also the sensory symptoms of irritation of the typical spontaneous attack of tetany are obtained when these phenomena are precipitated. The spontaneous attack of tetany is, in fact, reproduced in detail. One may therefore expect to be able to find a single explanation of all three phenomena. It seems desirable, therefore, to give first a brief survey of the spontaneous symptoms of tetany.

As is well known, the various symptoms of irritation in an attack of tetany manifest themselves in the following sequence: First of all, tingling sets in around the mouth and, peripherally, in the extremities. The tingling then increases in intensity, while it spreads proximally up over the extremities and over the face. Somewhat later a sensation of tension or spasm appears in the muscles of the mouth, the hands and the lower portion of the legs. This sensation of spasm increases in intensity and spreads in the same way as the tingling. Somewhat later a tonic spasm sets in, commencing in the muscles in which the sensation of spasm first occurred. If the attack is aggravated, the spasms spread proximally up over the extremities to the trunk. Fasciculation in the muscles, verging on spasm, is common, though but little noticeable in man. Spasm in the laryngeal muscles may set in at an early stage, as may also epileptic fits. The last-mentioned symptom, however, lies beyond the scope of this paper. As first shown by Grant and Gold-

From the Neurological Clinic and the Nobel Institute for Neurophysiology, Karolinska Institutet.

man,[1] active tetany can easily be induced experimentally by forced respiration.

The mechanism which produces these peculiar and spectacular symptoms has long been obscure. The results of the earlier experimental investigations on animals concerned with spasm and fascicular twitches are conflicting (Mustard[2]; Carlson and Jacobson[3]; Paton, Findlay and Watson[4]; Luckhardt, Sherman and Serbin[5]; Spiegel and Nishikawa[6]) and need not be summarized here. All the observations seem to show that the spasm is dependent for its full development on the integrity of tracts high up in the central nervous system.

Observations and deductions differing from those of the authors just referred to were made by West[7] in an extensive study on parathyroidectomized dogs. He classified the motor manifestations of parathyroid tetany in dogs as tonic, clonic and fibrillary. By "fibrillary" he meant repeated rapid contractions of small groups of muscle fibers. Since then Denny-Brown and Pennybacker[8] have defined fibrillation as contractions of individual muscular fibers, whereas West's term seems to correspond most closely to what is now called "fasciculation."

West found that all motor elements remained intact in the hindlegs if the spinal cord was transected in the dorsal or the cervical region. "Fibrillary" tetany, or fasciculation, was retained after section of the peripheral nerve; tonic tetany was not. Tonic tetany likewise ceased after deafferentiation by transection of the dorsal roots and was thus dependent on the integrity of the lowest spinal reflex arc. From these observations he drew the conclusion that parathyroid tetany arises essentially from the action of a circulatory factor peripherally on some site in the muscle to cause contractions of individual muscle fibers. Owing to

1. Grant, S. B., and Goldman, A.: A Study of Forced Respiration: Experimental Production of Tetany, Am. J. Physiol. **52**:209, 1920.

2. Mustard, H. J.: A Study of Certain Tonic and Reflex Nervous Impulses as Factors in Parathyroid Tetany, Am. J. Physiol. **29**:311, 1912.

3. Carlson, A. J., and Jacobson, C.: Further Studies on the Nature of Parathyroid Tetany, Am. J. Physiol. **28**:133, 1911.

4. Paton, D. N.; Findlay, L., and Watson, A: Tetania Parathyreopriva: The Parts of the Central Nervous System Involved, Quart. J. Exper. Physiol. **10**:233, 1916.

5. Luckhardt, A. B.; Sherman, M., and Serbin, W. B.: On the Origin of the Muscular Tremors, Clonic and Tonic Spasms in Parathyroid Tetany, Am. J. Physiol. **51**:187, 1920.

6. Spiegel, E. A., and Nishikawa, Y.: Der zentrale Mechanismus der Tetaniekrämpfe und ihre Beziehungen zur Enthirnungsstarre, Arb. a. d. neurol. Inst. a. d. Wien. Univ. **24**:221, 1923.

7. West, R.: Studies in Neurological Mechanism of Parathyroid Tetany, Brain **58**:1, 1935.

8. Denny-Brown, D., and Pennybacker, J. B.: Fibrillation and Fasciculation in Voluntary Muscle, Brain **61**:311, 1938.

an interplay of nerve impulses requiring an intact spinal reflex, the essential, or "fibrillary," tetany is converted into its tonic form.

In experiments on frogs and cats, Kuffler [9] recently studied the motor symptoms of tetany, which in these animals, according to him, are dominated by true fibrillation, as distinct from fasciculation, which he held to be due to impulses originating in the region of the end plates. He asserted it was probable that the motor symptoms of tetany were caused by impulses arising in synapses and end plates.

True fibrillation presumably occurs also in man, though it has not yet been observed or investigated. By means of electromyography, however, it should easily be shown if present. But the dominant sensory and motor phenomena of irritation associated with tetany, in man, as previously outlined, are primarily due to the effect of changes in the blood not on the muscle or the synapses but on the nerve itself, as I have shown [10] with the following, simple technic.

If a pneumatic cuff is inflated over the area of observation of the systolic pressure, just proximal to the elbow of the one arm, the muscles of the hand and about 40 cm. of the peripheral stretch of their nerve supply are excluded from the circulation and from the effect of changes in the blood. Nevertheless, on hyperventilation tingling, a feeling of tension and spasm set in with equal rapidity and with almost the same intensity in the two arms. Thus, in this case the muscle, the nerve endings and the peripheral part of the nerve can scarcely play any part in the production of the symptoms.

But if the cuff is moved higher and higher up the arm, the conditions will be crucially changed. It will be found increasingly difficult to induce symptoms of irritation in the ischemic arm. If the cuff is placed as high as possible, a spasm that cannot be controlled by volition will develop in the opposite arm before it can be produced in the ischemic one. Although all the symptoms of irritation can eventually be produced in the ischemic arm, they are throughout of far less intensity there. This can scarcely be interpreted otherwise than on the assumption that the impulses which give rise to the symptoms set out from, and can be most easily induced in, the proximal part of the peripheral stretch of nerve. Furthermore, the nerve fibers which first give rise to the impulses must be the longest ones in the extremities, since the symptoms begin at the periphery and spread centripetally.

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9. Kuffler, S. W.: Excitability Changes at Neuro-Muscular Junction During Tetany, J. Physiol. **103**:403, 1945.

10. Kugelberg, E.: (*a*) Accommodations och rheobasbestämningar i människans motoriska och sensibla nerver, Nord. med. **19**:1343, 1943; (b) Accommodation in Human Nerves and Its Significance for the Symptoms in Circulatory Disturbances and Tetany, Acta physiol. Scandinav., 1944, supp. 24.

Thus, in tetany the nerve is not affected uniformly along its entire course. This is indicated also by the fact that the electrical excitability was found to be increased to a much higher degree proximally than distally both in subjects with parathyroprivic tetany and in those with tetany due to hyperventilation. The fall of the rheobase and the poorer accommodation were more pronounced proximally. Moreover, it was found that when fasciculation occurred in a muscle whose motor nerve fibers were being tested electrically the accommodation was almost nil proximally while the rheobase was very low, an observation which indicates that spontaneous discharges were occurring in the tested region. A low rheobase and poor accommodation are the electrically measurable equivalents of "increased excitability."

The typical form of tingling associated with tetany was found to arise in fibers transmitting light touch. As shown by the above mentioned observations, the fasciculations originate in the motor fibers. Finally, the sensation of spasm is not caused, as might have been expected, by the muscular contraction.

If a pneumatic cuff is distended above the elbow on the one arm and the experimental subject begins to hyperventilate, it will be found after a while that spasms occur in both hands, with an intense feeling of cramp (Kugelberg [10b]). When the cuff has been kept on for twenty to thirty minutes, the motor fibers are paralyzed as a result of the ischemia, as are the tactile fibers and the fibers of muscle sense. Although the hand is limp and the sensation of touch, pressure and position have vanished, a peculiar, "fantom limb" sensation remains. It feels as though the hand were assuming the typical spastic posture and as though the muscles were equally contracted in the two hands. Thus the sensation of spasm cannot be produced at the periphery by the actual contraction, but is a paresthesia that originates in a discharge from the proximal part of afferent fibers, presumably the muscle afferent fibers.

The spasm is caused either by impulses from the hyperexcitable discharging motor fibers or, reflexly, by impulses from the afferent fibers in the same region of the nerve. The latter alternative would harmonize with West's observation on dogs that spasm is dependent on the integrity of the lowest reflex spinal arc. It would be permissible to generalize from the experiments on dogs with reference to man if the statement by Flick and Hansen [11] is correct that the spasm in the Trousseau phenomenon cannot be produced if the nerves are blocked proximal to the cuff, an observation which would show that the spasm is really a reflex. However, experiments now proceeding indicate that the

11. Flick, K., and Hansen, K.: Zur Elektrophysiologie sogenannter tonischer Verkürzungszustände quergestreifter Skelettmuskeln: Das Trousseausche Phänomen und die Pfötchenstellung bei der Atmungstetanie, Ztschr. f. Biol. **82**:387, 1925.

Trousseau spasm is not a mere reflex; hence the question whether the spontaneous tetanic spasm is a reflex or not must be left open for the present.

Thus, provided that the aforementioned observations are correct, the mechanism for the origin of the symptoms dealt with here may thus be summed up as follows: The changes in the blood increase the excitability of the nerve, i. e., lower the rheobase and abolish the accommodation. This gives rise to spontaneous discharges primarily in the proximal part of the longest nerve fibers, from which the focus spreads, with increasing aggravation of the symptoms. The spontaneous activity starts in the tactile fibers, from which the typical sensation of tingling originates, and somewhat later is set up in other afferent fibers, which produce the feeling of tension. About the same time it reaches also the motor fibers, giving rise to fasciculations. The spasm is caused either by the activity in the motor fibers or, reflexly, by the activity in the afferent fibers.

THE TROUSSEAU PHENOMENON

Where the impulses that give rise to the spasm in the Trousseau phenomenon originate is a question which has been much discussed (for a review of the literature see Nothman [12] and Lewis [13]). Recently, however, Lewis [13] and, independently, I [10] have shown that these impulses are produced by the effect of ischemia on, mainly, the proximal part of the nerves.

CASE 1.—V. O., a woman aged 36, who was suffering from parathyroprivic tetany following a strumectomy in 1933, was treated at the clinic. She had not received any effective treatment before her admission, on April 17, 1945, when she had fascicular twitches and a feeling of tension in the small muscles of the hand, as well as occasional tactile paresthesia in the fingers. The amount of calcium in the blood serum was then 5.2 mg. per hundred cubic centimeters. She was treated with dihydrotachysterol and improved rapidly. But when the treatment was suspended for a fortnight, she had a relapse. She was then placed definitely under treatment with a suitable dosage. The amount of calcium in the serum, as well as the excitability of the nerves, gradually underwent marked changes, and, concomitantly, the Trousseau phenomenon could be elicited with comparative ease. Good facilities for studying the phenomenon were thus afforded.

Symptoms.—It was at first found that when the Trousseau phenomenon was precipitated all the sensory and motor phenomena in the spontaneous attack of tetany were reproduced, and in exactly the same way as regards sequence and spread.

The first symptom was tingling in the finger tips, spreading centripetally toward the place of compression. A few tenths of a second after the tingling had set in the feeling of tension in the muscles of the hand began, and at about the same time, but usually somewhat prior to its appearance, fasciculation started

12. Nothman, M.: Tetanie, in Bumke, O., and Foerster, O.: Handbuch der Neurologie, Berlin, Julius Springer, 1937, vol. 15, p. 173.

13. Lewis, T.: Trousseau's Phenomenon in Tetany, Clin. Sc. **4**:361, 1942.

in the same muscles. The feeling of tension increased and spasm began in the muscles of the hand. When the spasm had been well established, the fascicular twitches could no longer be observed. The feeling of tension and the spasm then spread, possibly up to the muscles of the forearm. The culmination of the intensity and spread of all the symptoms of irritability was reached in two to four minutes. The intensity then diminished, and the area of distribution decreased in reverse order of that of involvement. After seven to nine minutes all the symptoms of irritation ceased, likewise in reverse order of that of their occurrence.

When, at the time of the patient's admission to the clinic, the various symptoms of irritation were most pronounced, they set in, with intervals of a few seconds, after about ten seconds' compression of the upper portion of the arm. The first motor symptom was fasciculation in the muscles of the hand, so intense that it looked as though their surfaces were seething; it was rapidly followed by tonic spasms in these muscles. The thumb was first adducted, and this was immediately followed by flexion of the fingers at the basal joints and extension at the other joints. The muscular contractions were so strong that the patient could not execute any voluntary movements of the fingers and wrist. The tingling spread up to the cuff, which was applied to the middle of the upper portion of the arm. The cuff had to be removed after the lapse of a few minutes, owing to intense pain in the contracted, ischemic muscles.

As the patient's condition improved, the symptoms of irritation diminished in intensity, and their range of distribution decreased. They set in somewhat later than before, viz., after the lapse of one to one and a half minutes, and wore off sooner. The last motor symptom that remained was fasciculation in the muscles of the hand. At the same time, the tactile paresthesia was felt up to the knuckles. In the next stage the tactile paresthesia was the only remaining symptom of irritation. After additional administrations of dihydrotachysterol, the tingling also finally vanished.

The table shows the course of the process in relation to the blood calcium and the rheobase, as well as the accommodation in the ulnar nerve, which was stimulated proximal to the elbow, with a minimal twitch in the first dorsal interosseus muscle as an index. The place of stimulation on the nerve was the point of the lowest threshold, which was carefully determined, whereupon the spot was marked. The electrode was fixed with some strips of plaster (for technic, see Kugelberg [10b]). In all subsequent determinations, the electrode was then placed on the same mark, care being taken that the experimental subject always kept the arm in the same position, with a view to comparable values.

It should be pointed out that not only the spasm but also all the symptoms of irritation dealt with here arose in the proximal part of the ischemic nerve. This was ascertained with the same technic as that adopted for study of the spasm and tingling. Thus, the fasciculation associated with the Trousseau phenomenon is not caused by irritation of the muscle or the nerve endings but is produced by irritation of the nerve itself.

Changes in the Rheobase of the Nerve During Ischemia and Its Relation to the Phenomena of Irritation.—When the muscle is contracted

during the tonic stage, the threshold of excitation cannot be determined. This limitation, however, is of no consequence, as the threshold can be correlated with the fasciculation which precedes the spasm. Moreover, unduly high values for the rheobase are obtained when intense fasciculation is proceeding in the muscle. In fact, the minimal twitch, adopted as an index, cannot be observed in the midst of the general activity; hence, a more marked twitch with a somewhat higher threshold must be taken instead as an index.

The cuff was placed as high up on the arm as possible, in order to avoid affecting the position of the electrode at the elbow and changing the rheobase. Since fasciculation, as well as all the other symptoms of irritation, sets in more rapidly the farther proximally the cuff is placed, the changes in the rheobase as measured at the elbow cannot be directly correlated with the time of manifestation of the fasciculations, which in this case set in much farther proximally. The changes in

Tabulation of Data for V. O. on Different Dates

Date (1945)	Blood Calcium, Mg./100 Cc.	Rheobase, ma.	Accommodation Slope *	Spontaneous Symptoms of Irritation	Fully Developed Symptoms of Irritation on Compression 15 Cm. Proximal to Elbow
4/17	5.2	0.35	About 0	Tingling and fasciculation in hands	Tingling and intense spasm up to site of compression
4/20	...	0.9	17	None	Tingling up to wrist; slight spasm in hand muscle
4/24	8.2	1.8	18	None	None
4/27	...	1.6	17	None	Tingling in finger tips
5/ 2	7.0	1.2	18	None	Tingling up to knuckles; fasciculation and tension in hand muscles

* By the term "accommodation slope" is meant the slope of the straight portion of the curve showing the relation of the number of rheobases necessary for a threshold muscular contraction to the duration of the slowly rising current stimulating the nerve of the contracting muscle (Kugelberg [10b]).

threshold were correlated, instead, with the time of incipience and cessation of fasciculation in the other arm, where they had been elicited by compression above the elbow at a level corresponding to the position of the stimulating electrode. The results of three determinations of the rheobase during ischemia, made on different days with differing amounts of blood calcium and initial values of the rheobase, as well as varying intensities of the symptoms of irritation during ischemia (table), are shown in chart 1.

It will be seen from the chart that the electrical excitability, measured in terms of the rheobase, rapidly increases after ischemia (the rheobase decreases) for some tenths of a second, as has previously been observed in association with oxygen deficiency in nerves in vitro by Thörner,[14]

14. Thörner, W.: Ueber das Eregungsstadium der Erstickung und Narkose, Arch. f. d. ges. Physiol. **204**:747, 1924.

Heinbecker,[15] Lehmann [16] and others and as observed with ischemia in situ in experimental animals by MacCallum,[17] Paton and associates [4] and Morris,[18] and in man by Kugelberg [10], and, with respect to sensory fibers, by Thompson and Kimball.[19]

The excitability reaches its maximum after the lapse of about three minutes and then diminishes to pass the initial value, in this case after ten to twelve minutes. The absolute value reached by the increase in excitability is evidently determined by the initial value of the rheobase, which, in turn, as generally supposed, is determined by the amount of ionized calcium. The lower the rheobase in a given case, the lower

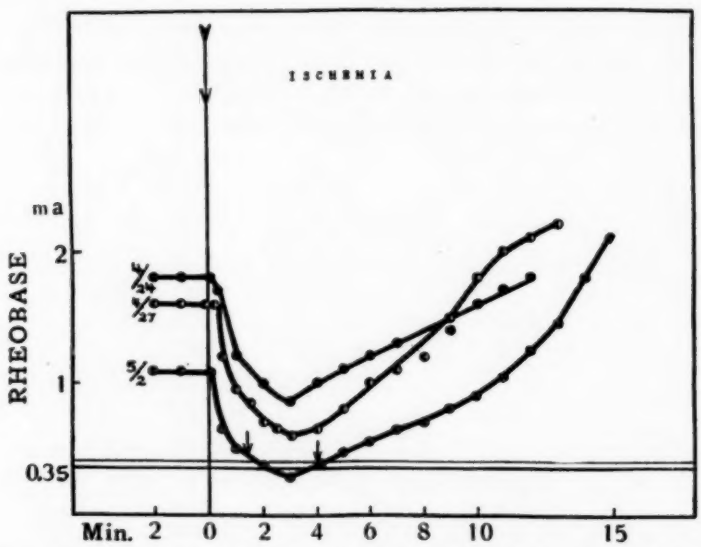

Chart 1.—Threshold curves during ischemia obtained from the ulnar nerve on stimulation at the elbow, with a minimal observed twitch in the first dorsal interosseus muscle as an index. The patient (V. O.) was tested on different days with different values for the blood calcium and the rheobase and with various symptoms of irritation caused by ischemia (table).

The double horizontal line indicates the threshold when spontaneous activity arises in the tested nerve fibers by diminution of the blood calcium. The arrows indicate the time when the spontaneous activity due to ischemia begins and ceases at the tested point.

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15. Heinbecker, P.: Effect of Anoxemia, Carbon Dioxide and Lactic Acid on Electrical Phenomena of Myelinated Fibers of the Peripheral Nervous System, Am. J. Physiol. **89**:58, 1929.

16. Lehmann, J. E.: The Effect of Asphyxia on Mammalian A Nerve Fibers, Am. J. Physiol. **119**:111, 1937.

17. MacCallum, W. G.: Ueber die Uebererregbarkeit der Nerven bei Tetanie, Mitt. a. d. Grenzgeb. d. Med. u. Chir. **25**:941, 1913.

18. Morris, N.: Anoxemia and the Increased Electrical Excitability of the Neuromyone, Brit. J. Exper. Path. **3**:101, 1922.

19. Thompson, M., and Kimball, S.: Effect of Local Ischemia upon Human Nerve Fibers in Vivo, Proc. Soc. Exper. Biol. & Med. **34**:601, 1936.

will be the level to which it falls; or, in other words, the less the amount of ionized calcium, the higher will be the increase in excitability.

If the changes in threshold are correlated with the general symptoms of irritability, it is evident that these symptoms will manifest themselves precisely during the period of increased excitability. They appeared, as before stated, after the lapse of ten seconds to one and a half minutes and wore off three to nine minutes later. They reached their culmination approximately in from two to four minutes, a period which corresponds to the maximum for the increase of excitability; and, like the latter, their intensity was determined by the original value for the rheobase and the ionized calcium. The correlation, however, will be still more exact if only the motor threshold is correlated with the fasciculation.

Fasciculations manifested themselves spontaneously at a blood calcium level of 5.2 mg. per hundred cubic centimeters and a rheobase of 0.35 milliampere. As accommodation at the same time was absent, there are good reasons for assuming that the fasciculations had appeared also at the point of determination. When the rheobase rose to 0.4 milliampere, they vanished. During ischemia, on the other hand, fasciculations likewise did not manifest themselves until the rheobase had fallen to 0.42 milliampere, and they ceased at approximately the same value, 0.38 milliampere (test on May 2, chart 1). From this it may be inferred that when the increase in excitability reaches a certain crucial value at a given point, spontaneous activity will manifest itself in the nerve fiber. This value can be attained by a diminution in the amount of ionized calcium, as in the spontaneous attack of tetany, or by ischemia. The intensity of the spontaneous activity during ischemia is determined by the amount of calcium in the blood. (A similar effect was described by Lehmann [16] on cat nerve in vitro during asphyxia.) At high values for the blood calcium in man no activity at all occurs. Normally, it occurs in the longest tactile fibers. On diminution of the blood calcium, activity develops in other afferent fibers, the motor fibers and the shorter tactile fibers, giving rise to a sensation of tension, the Trousseau phenomenon, fasciculations of varying intensity and the spread of tactile paresthesia.

VON BONSDORFF PHENOMENON

Von Bonsdorff [20] described a symptom for the diagnosis of latent tetany. He inflated a pneumatic cuff over the area of determination of the systolic pressure on the upper portion of the arm and kept it on for ten minutes. It was then removed, and the patient was told to hyperventilate. In the previously ischemic arm the typical tetanic spasm was then produced earlier than in the other arm—in cases of latent tetany even

20. von Bonsdorff, B.: Några fall av tetani bland värnpliktiga, Finska läk.-sällsk. handl. **72**:108, 1930.

after a few minutes or after a few deep breaths. In certain cases the phenomenon could be rapidly induced even when the Chvostek, Trousseau and Erb phenomena could not be elicited, and he found it to be a valuable supplementary sign in the diagnosis of tetany.

CASES 2 and 3.—Two patients suffering from tetany were treated at the clinic. K. D., a man, and B. S., a woman, had been admitted because of attacks of tetany which had been produced mainly by hyperventilation. In the case of K. D. they had commenced in connection with trumpet blowing. Both the patients showed a slightly positive Chvostek phenomenon but negative Trousseau and Erb phenomena and normal values for the blood calcium. On hyperventilation, the typical spastic posture of the hands manifested itself after the lapse of two to five minutes, being equally pronounced on the two sides. Thus, though these patients normally had no definite signs of imbalance of the calcium ions, which determines the excitability of the nerve (the alkali reserve, however, was not determined), symptoms of active tetany had manifested themselves with abnormal rapidity on hyperventilation. This experience, which had brought them to the hospital, shows the usefulness of hyperventilation tests in diagnosis in certain cases. Since the typical tetanic spasm had been rapidly induced on hyperventilation in both patients, they offered particularly good facilities for an analysis of the von Bonsdorff phenomenon.

Analysis of the Phenomenon.—Place of Precipitation: With compression of the pneumatic cuff over the area of determination of the systolic pressure, the whole arm (muscle, nerve endings and nerves) peripheral thereto is exposed to ischemia. In the phase of recovery from ischemia, changes in some of these tissues which tend to facilitate precipitation of the attack of tetany on hyperventilation evidently occur. In order to ascertain where the critical change originates, the experiment described in the following protocol was made.

Subject: K. D.

Preliminary test (Oct. 12, 1944): Hyperventilation. After four minutes spasms in both hands and in the region of the facial nerve on both sides set in simultaneously and with the same intensity.

Experiment A: A pneumatic cuff was distended to 200 mm. high up on the upper portion of the left arm.

Five minutes: A new cuff was placed around the lower part of the upper portion of the same arm and distended, and the upper cuff was removed. Hyperventilation was begun.

Six minutes: Spasm appeared in the left hand and in a few seconds could not be voluntarily controlled.

Nine minutes: Intense spasm continued in the left hand. Spasm appeared in the face. Paresthesia began in the right hand. Hyperventilation was discontinued.

Experiment B (Oct. 13, 1944): A pneumatic cuff was distended over the area of determination of the systolic pressure, just proximal to the elbow of the right arm.

Five minutes: The cuff was removed, and a new one was placed immediately above and distended, so that its lower edge lay on the site of the upper edge of the first cuff. Hyperventilation was begun.

Eight minutes: Spasm appeared in the left hand.

Thirteen minutes: Spasm continued in the left hand; none occurred in the right hand. Hyperventilation was discontinued.

Experiment A shows that for full development of the phenomenon it suffices if the hyperventilated blood is brought into contact with the proximal part of the previously ischemic nerve. If the flow of blood is blocked proximal thereto, the phenomenon, as is to be expected, does not appear (experiment B).

That the impulses which give rise to the phenomenon come mainly from the proximal part of the previously ischemic stretch of nerve can be shown in the following way: A pneumatic cuff is placed on each arm and distended and is kept on for five minutes. A new cuff is then distended around the upper part of one forearm, and the first cuffs are removed. When the experimental subject then begins to hyperventilate, the spasm sets in with about the same rapidity and intensity in the two hands. This shows that muscles, nerve endings and the peripheral stretch of nerve do not play any appreciable part in the precipitation of the phenomenon.

Optimal Place of Precipitation in the Arm.—Since sensitivity of the nerve to ischemia increases from the peripheral to the proximal part (Lewis, Pickering and Rothschild [21]) and since this applies also to the effect of those changes in the blood which give rise to tetany (see introductory section), it may a priori be expected that the von Bonsdorff phenomenon could be more readily precipitated the more proximally on the arm the cuff has been placed. This, in fact, proved to be the case. If the cuffs are placed at different levels on the arms and if they are kept on for the same length of time, it will be found on hyperventilation that the spasm will set in earliest and with greatest intensity on the arm on which the cuff has been placed more proximally. The phenomenon, however, can be precipitated also on the forearm, but it will be less pronounced and may require a longer preceding compression.

The Time Factor and Its Relation to Electric Excitability in the Nerve.—I further investigated how long after the removal of the pneumatic cuff the spasm is most readily induced in the previously ischemic arm. It was found, somewhat to my surprise, that if hyperventilation was deferred for ten to fifteen minutes after the removal of the cuff the appearance of the spasm was actually impeded if the cuff had been placed on the proximal part of the upper portion of the arm. This is illustrated by the following protocol.

21. Lewis, T.; Pickering, G. W., and Rothschild, P.: Centripetal Paralysis Arising Out of Arrested Bloodflow to the Limb, Including Notes on a Form of Tingling, Heart **16**:1, 1931.

Subject: B. D.

Preliminary test Nov. 20, 1944: Hyperventilation. The spasm set in simultaneously and with the same intensity in the hands in five minutes.

Experiment: A pneumatic cuff was placed as far proximally as possible on the right arm and was distended to 200 mm.

Ten minutes: The cuff was removed.

Twenty-five minutes: Hyperventilation was begun.

Thirty-two minutes: Spasm appeared in the left hand and could not be voluntarily mastered; no spasm occurred in the right hand.

Thirty-six minutes: Spasm continued in the left hand, but none appeared in the right. Hyperventilation was discontinued.

Forty-five minutes: Spasm ceased in the left arm.

These general relations were confirmed in several experiments. In chart 2 the change from increased to decreased sensitivity to hyper-

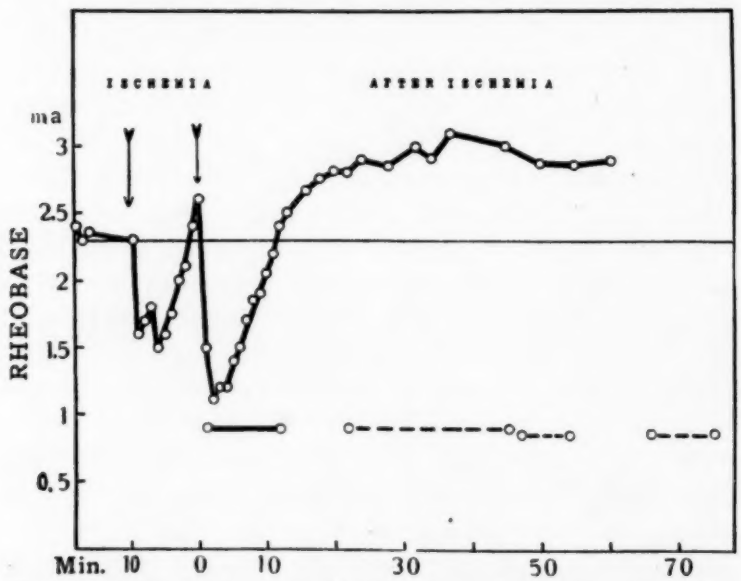

Chart 2.—Threshold curve obtained from the ulnar nerve after ischemia, showing relation to facilitation and inhibition of spasm induced by hyperventilation in the previously compressed arm.

The horizontal lines below the curve may be interpreted as follows: The solid line in the circles indicates duration of facilitation of spasm; the broken line with circles, the duration of inhibition of spasm.

ventilated blood is strikingly illustrated by the curve for the changes in the rheobase after ischemia.

The rheobase was determined on fibers to the first dorsal interosseus muscle in the ulnar nerve, which had been stimulated at the elbow. The determination was made on experimental subject B. S. before and after ten minutes of ischemia. Afterward, the test for the von Bonsdorff phenomenon was made, the subject beginning the hyperventilation at various intervals after the removal of the cuff. On each occasion the

hyperventilation was arranged in such a way that the spasm continued for about ten minutes. As shown in chart 2, the excitability of the motor nerve fibers was considerably enhanced on the removal of the cuff. This applies not only to the rheobase but also to the accommodation, which fell toward zero. At the same time the excitability in the sensory nerve fibers was doubtless likewise intensified, since spontaneous activity was set up in them causing the "pins and needles" paresthesia and the so-called pseudospasm (Lewis and associates [21]). After about ten to twelve minutes this increase in excitability was converted into a decrease, which probably continued for hours.

If, as shown in chart 2, the hyperventilated blood was brought into contact with the proximal part of the previously ischemic nerve during the stage of increased excitability, the von Bonsdorff phenomenon was induced. If, instead, the changed blood was brought into contact with the nerve during the stage in which the excitability was diminishing, the occurrence of all the symptoms of tetany was retarded. The von Bonsdorff phenomenon is evidently precipitated by a summation of the postischemic increase of the excitability in the nerve and that induced by hyperventilation, with resulting spontaneous activity, which gives rise to symptoms of irritability.

COMMENT

In the first few minutes during and after ischemia an increase of excitability exists in the nerve. The same effect is produced by the changes in the blood which give rise to tetany. When the excitability reaches a crucial value, the nerve begins to discharge spontaneously. The activity starts in the proximal part of the longest tactile fibers and then proceeds to somewhat shorter ones. When the resulting paresthesia has reached approximately the wrist or the middle of the forearm, the activity starts in the longest motor fibers and in other afferent fibers, presumably to muscle, and then passes to increasingly shorter fibers. This strict sequence in the appearance of spontaneous activity can scarcely be correlated in detail with any known physiologic or anatomic characters in the nerve itself.

Certain facts indicate that this phenomenon can be correlated with the thickness of the fibers. Evidently, it is connected with the large fibers. Moreover, the longest fibers transmitting light touch must be presumed to be thicker than the longest motor fibers, since, as shown in the ulnar nerve in man (Kugelberg [10]), they have a considerably lower rheobase. In order to fit in with this hypothesis, the muscle afferent fibers should have a thickness corresponding to that of the motor fibers; but for man no data are available on this matter.

The greater tendency to activity in the proximal portion of the nerve may be due to the fact that the individual nerve fibers taper toward

the periphery, owing to the branching of the fibers (Eccles and Sherrington [22], Björkman and Wohlfart [23] and others). Certain data indicate also that, as first stated by Schwalbe,[24] the longest fibers are thicker than the shorter ones. It remains to be shown that the longest and thickest motor fibers and muscle afferent fibers are thicker than the short tactile fibers. However, there are evidently so many gaps in the chain of evidence that it would be unwise at present to press the theory too far.

It should also be noted that localization of the spontaneous activity can be correlated with the tendency to respond with iterative discharges to a constant electric current. Thus, the threshold for prolonged iterative discharges is lower in tactile than in motor fibers and lower in long than in short motor fibers (Kugelberg [10]), as well as lower in the proximal than the distal portion of a motor nerve (Kugelberg and Skoglund [25]).

SUMMARY

The observations on the Trousseau and on the Bonsdorff phenomenon may be summarized as follows:

1. In the Trousseau phenomenon, all the symptoms of irritation in spontaneous attack of tetany are produced in identically the same way with regard to sequence and distribution. Tactile paresthesia, fasciculation, the sensation of spasm and the spasm itself appear in the order of enumeration. They begin peripherally and spread centripetally.

2. All the symptoms of irritation are caused by spontaneous activity, which appears first and foremost in the proximal part of the longest nerve fibers in the ischemic nerve. The activity starts in the tactile fibers, then proceeds in the motor fibers and about the same time appears in other afferent fibers. The spontaneous activity begins in from ten seconds to one and a half minutes, reaches its culmination in two to four minutes and passes off after ischemia of four to nine minutes' duration.

3. Ischemia increases the excitability of the nerve. This increase begins after a few seconds, reaches its culmination in about three minutes, whereupon it diminishes and, after the lapse of ten to twelve min-

22. Eccles, J. C., and Sherrington, C. S.: Numbers and Contraction-Values of Individual Motor-Units Examined in Some Muscles of Limb, Proc. Roy. Soc., London, s. B **106**:326, 1930.

23. Björkman, A., and Wohlfart, G.: Faseranalyse de Nn. oculomotorius, trochlearis and abducens des Menschen und des N. abducens verschiedener Tiere, Ztschr.f.mikr.-anat.Forsch. **39**:631, 1936.

24. Schwalbe, G.: Ueber die Kaliberverhältnisse der Nervenfasern, Leipzig, F. C. W. Vogel, 1882.

25. Kugelberg, E., and Skoglund, C. R.: To be published.

utes, reaches the same value as before the ischemia. The level reached by the increase is determined by factors in the blood. The smaller the amount of calcium (ionized calcium) in the blood, the higher the values, and vice versa.

4. The spontaneous activity is due to the increase of excitability of the nerve. When it reaches a certain crucial value in a given nerve fiber, spontaneous activity is produced. As shown for motor fibers, this occurs irrespective of whether the increase is produced by diminution of the blood calcium or by ischemia.

5. After preceding ischemia of the arm for ten minutes, the typical manifest symptoms of tetany induced with hyperventilation are facilitated in the same arm for about ten minutes and are then inhibited for at least an hour.

6. The attack of tetany is facilitated by a summation of the post-ischemic increase of excitability and that caused by hyperventilation, giving rise to spontaneous activity. The inhibition is due to the post-ischemic decrease of excitability.

7. The more proximal the portion of the arm which is subjected to ischemia, the more easily will the symptoms of hyperventilation tetany be induced.

8. The impulses which give rise to the symptoms of tetany in the von Bonsdorff phenomenon start first and foremost from the proximal part of the previously ischemic nerve. The focus for the attack of tetany produced by hyperventilation can thus be shifted from the proximal part of the course of the peripheral nerve distally to the desired stretch of nerve by previously subjecting the nerve to ischemia.

The sequence of the various symptoms of irritation in the spontaneous attack of tetany, the Trousseau and von Bonsdorff phenomena, is discussed in relation to the size of the fibers involved and their tendency to iterativeness on excitation with a constant current.

Nobel Institute for Neurophysiology, Karolinska Institutet.

CIRCULATION OF CEREBROSPINAL FLUID IN CARASSIUS GIBELIO

T. G. van RIJSSEL
GRONINGEN, NETHERLANDS

IN THE literature one finds various, and often controversial, opinions and observations concerned with the origin, movement, pathways, absorption and function of the cerebrospinal fluid. An excellent survey of this matter is found in the monograph of Katzenelbogen.[1] The literature gives ample proof that the formation of the fluid occurs in the choroid plexuses. Whether cerebrospinal fluid is also formed elsewhere (e. g., in the cerebrospinal parenchyma or in the ependyma) is a much debated question. According to Sepp [2] and others, the movement of the cerebrospinal fluid is produced by vascular pulsations; according to still other investigators, respiratory movements and movements of the body and the head are contributing factors. Concerning the relations between the cerebrospinal fluid and the perivascular and the pericellular spaces many opinions are in existence. The escape of the cerebrospinal fluid from the cerebrospinal cavity takes place by absorption into the veins, through the arachnoidal villi (Weed [3]), or by perineural transportation and absorption into the lymph spaces. With regard to the last point especially there exists a lively discussion.

It was the opinion expressed by Dr. H. Berkelbach van den Sprenkel, conservator of this laboratory, that there is fluid in the perivascular spaces of the brain and that this cerebrospinal fluid is moved by the pulse wave of the blood vessels and consequently flows in the same direction as the blood stream. Dr. Berkelbach van den Sprenkel advised me to

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From the Histological and Embryological Laboratory, University of Utrecht; Director, Prof. Dr. J. Boeke.

1. Katzenelbogen, S.: The Cerebrospinal Fluid and Its Relation to the Blood, Baltimore, Johns Hopkins Press, 1935. An extensive bibliography is included in this monograph.

2. Sepp, E.: Die Dynamik der Blutzirkulation im Gehirn, Berlin, Julius Springer, 1928.

3. Weed, L. H.: Anatomical Consideration of the Cerebro-Spinal Fluid, Anat. Rec. **12**:461, 1917; Experimental Production of Internal Hydrocephalus, Contrib. Embryol. **9**:425, 1920; Cells of the Arachnoid, Bull. Johns Hopkins Hosp. **31**:343, 1920; Absorption of Cerebrospinal Fluid into the Venous System, Am. J. Anat. **31**:191, 1923; Effects of Hypotonic Solutions upon Cell-Morphology of Choroid Plexuses and Central Nervous System, ibid. **32**:253, 1923. Weed, L. H., and Hughson: Cerebrospinal Fluid in Relation to the Bony Encasement of the Central Nervous System as a Rigid Container, Am. J. Physiol. **58**:85, 1921.

carry out experiments on fish, on the supposition that the complicated relations would be simpler to study in lower vertebrates. Nowhere in the literature have I found any communications on experiments concerned with the circulation of the cerebrospinal fluid in fish.

For my experiments I used Carassius gibelio (family, Cyprinidae), a kind of carp (*kroeskarper*), a common fish in the Netherlands, about 10 cm. in length. This animal proved very suitable for the experiments, since its brain is proportionally small and lies in a spacious skull. The ventricular system and the pericerebral spaces are wide, so that there is relatively a great quantity of cerebrospinal fluid; moreover, the brain is not easily injured by intracranial injection.

EXPERIMENTAL TECHNIC

Absorption Experiments.—In this series it was tried to produce absorption of dye by letting the fish swim for varying lengths of time (one-half to forty days) in solutions of trypan blue, of various concentrations. The fish were then examined histologically to see whether the dye could be found in the central nervous system or in its membranes. These experiments are cited as series 2. For these experiments I used 8 fish, 5 of which were examined in serial sections.

Intracranial Injections.—To trace the spread of the cerebrospinal fluid and to determine the pathways through which the fluid flows, dye was injected into the pericerebral space with a fine needle, usually in the occipital region. From 0.1 to 0.2 cc. of a 1 per cent solution of trypan blue or of a 5 per cent suspension of india ink in Ringer's solution was injected. Fourteen fish were used in these experiments. Some fish died in consequence of too deep a puncture, the cerebrospinal axis having been injured. Others survived this operation, were apparently healthy and were killed at various times after the injections (twenty-three minutes to eight days). Nine fish receiving such injections were examined in serial sections.

A series of sections was also made of a normal fish which had not undergone any previous treatment.

The rest of the technical procedure was as follows:

The head was fixed in Bouin's fluid (often after removal of the lower jaw and the gills); it was then decalcified in 10 per cent trichloroacetic acid for about ten days and embedded in paraffin (via the alcohols; methylbenzoate and pyroxylin benzene, and benzene and paraffin). The resulting blocks were cut serially, and alternate sections were stained with carmalum and hematoxylin and eosin.

The body was cut in slices and also fixed, embedded, sectioned and stained. At various levels transverse sections were selected for examination.

There is no need to describe all the series of sections separately, as microscopic examination showed that the results of similar experiments were in agreement.

Experimental data on 2 fish, which are referred to later, are given here.

FISH III B.—One-tenth cubic centimeter of a 1 per cent solution of trypan blue was injected intracranially in the occipital region near the median line; the fish was not very lively; it was killed twenty-four minutes after the injection.

FISH VII A.—Two-tenths cubic centimeter of a 5 per cent suspension of india ink in Ringer's solution was injected intracranially in the occipital region near the median line. The behavior was fairly normal; the fish was killed eight days after the injection.

OBSERVATIONS

ABSORPTION EXPERIMENTS (SERIES 2)

The fish proved to be just able to stay alive when swimming in aqueous solutions of trypan blue in concentrations from 0.05 to 0.1 per cent.

In more concentrated solutions they died. Histologic examination revealed the blue dye in the gills; the mucous membranes of the mouth; palate; skin canals; intestine; the blood vessels in the wall of the intestine; the myocardium; the kidneys; the periosteum of the vertebrae, and the endothelial cells of the liver and pancreas. This makes it evident that dye had been absorbed and had entered the circulating blood. Considering the blue dye in vessels of the intestinal wall, it is probable that this absorption took place in the intestine. No trace of dye was found in the central nervous system or in its membranes. Obviously, the dye did not pass through the blood–cerebrospinal fluid barrier in sufficient amounts to be detected.

That no blue dye was observed in the central nervous system is not absolute proof that a barrier exists between the blood and the cerebrospinal fluid. It is still possible that the concentration of the dye in the central nervous system was too low for the blue color to become visible.

Also using Carassius, Wislocki [4] gave intraperitoneal injections of the solutions of trypan blue. He detected the dye microscopically in the reticuloendothelial system of many internal organs (liver, spleen, kidney), in the endothelium of lymph vessels and as a diffuse blue stain of the tissues. He stated emphatically that only in the central nervous system did he fail to find any blue dye. Presumably, in his experiments the concentration of dye in the blood was higher than in mine, whereas in my fish the blue dye was in the circulation a much longer time.

As it was impossible to detect trypan blue in the central nervous system after the dye had been introduced into the circulating blood by various methods (series 2 of the present study and the experiments of Wislocki), it is permissible to conclude that in Carassius gibelio there exists a blood-cerebrospinal fluid barrier with respect to trypan blue.

INTRACRANIAL INJECTION

Pericerebral Space.—Between the brain and the skull a wide space exists. Close to the brain lies a thin membrane, containing many blood vessels. Outside this membrane is a free space, which is surrounded by a tissue extending to the skull. It was repeatedly evident

4. Wislocki, G. B.: Action of Vital Dyes in Teleosts, Anat. Rec. **12**:415, 1917.

that there had existed connections between this tissue and the membrane surrounding the brain. Therefore the free space is to be taken, for the greater part at any rate, as the result of shrinkage.

The pericerebral tissue, extending from the membrane around the cerebrum to the skull, has a peculiar structure. It consists of flat cells, forming strands and partitions. In this manner the pericerebral space is divided into chambers and meshlike spaces. Herein lies the tissue fluid, which locally has a mucous or fatty character (Coupin [5]). This pericerebral tissue has a definite architecture. At the level of the olfactory tract a tissue with small chambers lies against the inner side of the skull, whereas centrally in the cranial cavity spacious cisterns are present. In general, one sees in the dorsal part of the cranial cavity a tissue with small chambers; nearer the brain the spaces are wider; next to the brain the tissue often has a meshlike structure. Lateral and basal to the brain is also wide-meshed tissue. Likewise, along the labyrinth the tissue is very delicate. At the level of the medulla oblongata it consists only of some protoplasmic strands lying in the pericerebral space. Within the first vertebral arch on the ventral side of the spinal cord a stiff fibrous tissue arises from the adventitia of the basal blood vessels in the meninx. This stiff fibrous tissue extends laterad and dorsad until the cord lies enclosed in a close-fitting shell (fig. 6 *F*). At this point the meshlike tissue has nearly disappeared. About 500 microns more caudal the fibrous tissue is again found in only the ventral region. Now the cord lies once more in the usual meshlike tissue.

From the injection of dye into the pericerebral tissue it was ascertained that the dye spreads swiftly through the chambers and meshes of the pericerebral tissue. This spread was swiftest and the dye most dense where the tissue was of a meshlike structure or where the tissue chambers were spacious—consequently near the brain. Yet I noted repeatedly in animals killed about twenty minutes after the injection that in the small chambers near the skull the coagulum of the mucous tissue fluid was already blue throughout. Hence, injected dye spreads quickly through the pericerebral tissue. It is evident, therefore, that many opportunities exist for exchange of fluids in the meshes and chambers in the various parts of the tissue lying between the brain and the skull.

In all animals it was obvious that the dye, injected into the pericerebral tissue, spread immediately through the whole ventricular system, the roof of the fourth ventricle not having been injured by the injection. Thus it is evident that an extensive exchange of fluid must take place between the ventricular system and the meshes and chambers of the pericerebral tissue.

5. Coupin, F.: Les formations choroïdiennes des poissons, Arch. de morphol. gén. et expér., 1924, no. 20, pp. 1-156.

The particles of dye in part lay free in the ventricles and in the spaces of the pericerebral tissue and in part were phagocytosed by histiocytes. In determining the spreading of the dye, one has to take into consideration that histiocytes, having phagocytosed the particles of dye, can wander everywhere. Only the spread of free dyestuff gives an indication of the spread of cerebrospinal fluid.

Thus, the experiments with intracranial injection prove that a close connection exists between the ventricular fluid and the contents of the meshes and chambers of the pericerebral tissue, that the meshes and chambers of this tissue communicate with each other and that fluid can flow through them. Hence, the relations in Carassius gibelio are in principle the same as those in higher vertebrates: The ventricular system contains a fluid (liquor internus); and the brain is surrounded with a fluid (liquor externus), which flows through the meshes of the pericerebral tissue (meninx). This pericerebral fluid and the ventricular fluid are closely related.

Ariëns Kappers,[6] in agreement with Sterzi, spoke of a meninx primitiva in teleosts, since he found no differentiation of pia, arachnoid and dura in these forms and the meshlike tissue has no endothelial covering, as exists in a true arachnoid. Between the skull and this meninx primitiva he still discerned a perimeningeal tissue, and in some teleosts (Lophius) he described a kind of dural membrane as well.

In an extensive treatise, van Gelderen[7] explained that in most teleosts an ectomeninx lines the skull and an endomeninx covers the brain and that between them lies an intermeningeal tissue, of a mucous or fatty character. I found the pericerebral tissues of Carassius to be in accordance with this description.

Ariëns Kappers[6] also stated emphatically that as there is no arachnoid there can be no external fluid. This last opinion one encounters repeatedly in the literature (Coupin, among others). To my mind, Ariëns Kappers is in error in refusing to call the fluid which flows in the meshes and chambers of the pericerebral tissue, and which is closely related to the ventricular fluid, liquor externus because the tissue morphologically does not quite correspond with the arachnoid. Even if the pericerebral tissue does not quite correspond morphologically with the leptomeninges of the higher vertebrates, it has no doubt the same

6. Ariëns Kappers, C. U.: Meninges in Lower Vertebrates, Arch. Neurol. & Psychiat. **15**:281 (March) 1926. Ariëns Kappers, C. U.; Huber, G. C., and Crosby, E. C.: Comparative Anatomy of the Nervous System of Vertebrates, Including Man, New York, The Macmillan Company, 1936.

7. van Gelderen, C.: Ueber die Entwicklung der Hirnhäute bei Teleostiern, Anat. Anz., **60**:48, 1925; Die vergleichende Ontogenie der Hirnhäute, mit besonderer Berücksichtigung der Lage der neurokraniellen Venen, Thesis, Amsterdam, Munich, J. F. Bergmann, 1926.

significance. Therefore, I shall designate as meninx all the tissue between the skull and the brain in the meshes and chambers of which flows a fluid in close relation to the ventricular fluid. The meshes and chambers together constitute the meningeal space.

Roof of the Fourth Ventricle.—Although apparently an extensive exchange of fluid takes place between the internal and the external fluid, the roof of the fourth ventricle seems to be continuous, and no open foramen (of Magendie or of Luschka) is found here. But at various places in this region the roof has become a very thin membrane, outwardly consisting of the inner meningeal membrane and inwardly lined with ependyma. The ependyma is very flat here, and at many places it cannot be decided whether an ependymal lining still exists or whether the few flat cells which form the roof are meningeal. However, in some places the ependymal lining is plainly interrupted for some distance, so that actually the ventricular roof consists of meninx only. Hence, if the meninx were taken away, openings would be left in the roof. It is probable that this very thin roof gives opportunities for the exchange of fluid between the ventricle and the meningeal space (fig. 5 *H*).

Roof of Third Ventricle.—That connections exist elsewhere between the ventricle and the meningeal space was apparent, among other specimens, in fish III B. The greater part of the roof of the third ventricle was very thin and consisted almost exclusively of ependyma, outwardly covered by the inner membrane of the meninx. At many places blue lines were seen between the high ependymal cells; therefore a continuity existed between the blue coloring matter in the ventricle and that in the meningeal meshes. I observed this, for example, at the level of the corpora striata and close to the tori longitudinales, just anterior to the cerebellum. Of course, my sections do not answer the question about the direction of passage of the fluid through the roof, but they do prove that at these places communication exists between the internal and external cerebrospinal fluid (fig. 5 *K*).

The roof of the third ventricle is lined with several kinds of ependymal cells. (It is strange that nothing can be found about these various forms of ependyma in Coupin's article, notwithstanding his extensive study of the ventricular roofs and plexuses in fishes). Laterally, the ependymal cells are very flat (although not so flat as those in the roof of the ventricle); medially there is a region with high cylindric ependymal cells. Close in front of the posterior commissure a tube arises from the roof. This tube extends forward in the median line and at the level of the bulbi olfactorii becomes a flat organ, lying close under the skull. This organ is the epiphysis cerebri (Brachet [8]).

8. Brachet, A.: Traité d'embryologie des vertébrés, ed. 2, Paris, Masson & Cie, 1935, p. 376.

Choroid Plexus of Third Ventricle.—In front of the pineal tube the roof is strongly folded, and it projects dorsally as a sac which encloses the pineal tube. This sac is the choroid plexus of the third ventricle. Its walls have many folds and are lined with a cuboid, or simply a cylindric, epithelium, often with vacuoles at the apex. The bases of the epithelial cells border immediately on the walls of many wide capillaries, which are lying here in the meninx. Repeatedly, the capillaries project into the epithelial layer between the cells, so that the lumen of the blood vessel and the space in the plexus sac are separated only by an extremely thin strip of protoplasm. I found such interepithelial capillaries also in the pineal tube and in the medial part of the roof of the third ventricle.

Choroid Plexus of the Fourth Ventricle.—This structure lies medially in the ventricular roof. The roof here is folded, and the folds hang downward in the ventricle. The epithelium of the plexus is cylindric, and the cells are somewhat higher than those in the plexus of the third ventricle. Immediately beneath the epithelial layer, many blood vessels lie in the meninx which accompanies the folds.

Absorption in Choroid Plexus.—From the literature, it is apparent that the formation of the cerebrospinal fluid occurs in the choroid plexus. Some authors think that absorption occurs also in the plexus. My sections give support to this last opinion.

In fish III B, many veins of the choroid plexus of the fourth ventricle which lay against the epithelial layer contained a strongly blue-stained coagulum of plasma, whereas in the immediate vicinity of these veins no important concentration of dye was seen. In other veins, in the meninx, one seldom saw such a blue coagulum, and then only when much dyestuff was lying in the surrounding meningeal tissue.

In fish VII A the epithelial cells of the plexus of the fourth ventricle which were lying in the tops of the folds contained a considerable number of india ink granules, (fig. 1 and fig. 5 *J*). The cells that contained the granules were those cells which were chiefly in contact with the ventricular fluid and so had the best opportunity of absorbing carbon particles from the internal cerebrospinal fluid. The assumption of absorption appears to me to be the only possible explanation of this peculiar distribution of the granules in the epithelium of the plexus, and the local accumulation of trypan blue in the veins is difficult to explain in any other way.

As to the choroid plexus of the third ventricle, my sections are less convincing. In fish VII A, the epithelium of the plexus of the third ventricle contained much less carbon than that of the plexus of the fourth ventricle; yet there were also fine carbon granules in the epithelium of the plexus sac, much finer than in the plexus of the fourth ventricle. Also, in the roof of the third ventricle similar fine

particles were to be found in the flat, as well as in the high, ependymal cells. On the inner and on the outer side of the roof of the third ventricle, as well as in the ventricle itself and in the meningeal space, carbon particles were lying. Consequently, it is not possible to decide whether the granules in the ependymal cells were absorbed from the internal cerebrospinal fluid or whether they were carried from the meninx to the ventricle. In fish III B, a blue hue was noted in some of the veins of the plexus and in the ventricular roof.

I think that it is permissible to conclude, therefore, that the epithelial cells of the choroid plexus of the fourth ventricle absorb colloidal particles from the internal cerebrospinal fluid and release these particles into the blood. My sections do not permit a conclusion as to

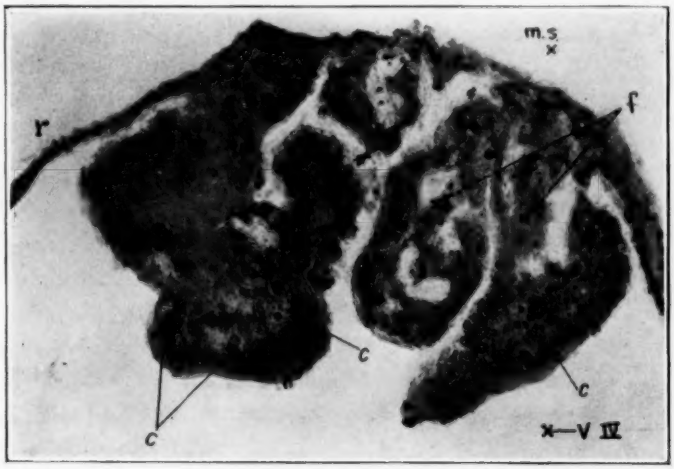

Fig. 1 (fish VII A; section 72, I, 6).—Section (about × 400) showing the choroid plexus of the fourth ventricle.

Here, *ms* indicates the meningeal space; *r*, the thin roof of the fourth ventricle, lined with low ependymal cells; *f*, folds of the roof, covered with high epithelial cells and hanging into the ventricle; *V IV*, lumen of the fourth ventricle, and *c*, carbon particles stored in the epithelial cells.

It is evident that the dye is stored in those epithelial cells that are most in contact with the ventricular fluid. Probably absorption from the internal cerebrospinal fluid takes place in these cells (cf. fig. 5 *J*).

whether particles are absorbed from the cerebrospinal fluid by the choroid plexus and by the roof of the third ventricle.

Perivascular Spaces.—The blood vessels in the brain are surrounded by spaces which are continuations of the pericerebral space. Like the meningeal space, these perivascular spaces are traversed by fine tissue strands, so that they have a meshlike structure. The perivascular spaces are also distinctly visible around the small vessels, but it cannot be decided whether or not they are still virtually present around the smallest vessels and capillaries.

In all my specimens, communication existed in many places between the ventricular space and the perivascular spaces of vessels lying just beneath the ependyma. This communication was effected by interruptions in the ependymal layer. The blood vessels were then often nearly intraependymal. These open communications were most distinct in the optic tectum. It is evident that these communications gave opportunity for the exchange of fluid between the internal cerebrospinal fluid and the contents of the perivascular spaces. This exchange was demonstrated by the intracranial injections.

It was observed repeatedly that the dye had penetrated from the ventricular space through the open communications into the perivascular space of the subependymal blood vessels. It is apparent, especially in the case of the carbon granules, that the particles of dye were carried along in the perivascular spaces in the same direction as that in which the blood flowed in the vessel. If one follows an artery whose perivascular space communicates with the ventricle, beginning at the point of this communication and going downstream, one still sees carbon particles lying around the vessel and its branches in many sections after the artery has left the neighborhood of the ventricle. Sometimes 40 sections (of 10 microns each) beyond the point of communication dye is still present in the periarterial space. If one follows this artery in the opposite direction, or upstream, it appears that the dye has hardly been carried along at all. Three or four sections in front of the communication of the ventricle with the perivascular space there are no longer any carbon particles around the vessel (fig. 5 *F*). Hence, the dye particles have been carried in the perivascular space in the same direction as that in which the blood flows in the vessel, whereas no dye has been carried in the opposite direction.

I saw a similar picture around veins. In fish VII A, several venous branches in the optic tectum joined and formed a small vein, just beneath the ependyma. Soon there was an open communication between the ventricle and the perivenous space. Here the ventricle contained many carbon particles, which entered the perivenous space at the point of communication and from there were seen around the vessel. Then the vein left the region of the ventricle and passed through the optic tectum, still surrounded with dye. Then, it opened into the venous network of the meninx on the surface of the brain, while the perivascular space opened into the meningeal space (fig. 5 *E*). Here, therefore, the perivenous space formed a direct junction canal between the ventricle and the meningeal space, and, again, dye was carried in the direction of the blood current, that is, from the ventricle to the meninx. Of course, all the periarterial spaces which communicate with the ventricle also form such junction canals. In these spaces, the fluid flows from the meninx to the ventricle (fig. 5 *C*).

It is curious that in all my fish arteries were observed lying just beneath the ependyma; these gave off branches penetrating the ependymal layer. These arterial branches ran right through the ventricular space toward the cerebellum, which projects here into the ventricle. They entered the cerebellum, where they ramified. At the point where they passed through the ventricular space these arteries were not covered with an ependymal layer: Ventricular fluid flowed around the adventitia. The perivascular spaces of these arteries opened into the ventricle where the vessels passed from the cerebrum into the ventricle and where the vessels left the ventricle and entered the cerebellum. Here, too, in fish VII A, carbon particles were carried from the ventricle into the perivascular spaces in the direction of the blood current, and so into the cerebellum (fig. 5 *G*). Charlton [9] gives a figure showing a transventricular blood vessel in a viper. He did not mention the behavior of the perivascular space.

It has already been noted that the perivascular spaces communicate with the meningeal space (page 530), being, as it were, continuations of the latter. It is obvious that the external cerebrospinal fluid and the perivascular fluid are closely related. The transportation of particles of dye here is interesting. They penetrated from the meningeal space into the perivascular spaces of arteries entering the brain and were observed deep in the cerebrum around these vessels and their branches. Here, too, then, dye was transported in the direction of the blood current (fig. 2 and fig. 5 *B*). In the perivascular spaces of veins leaving the brain and entering the meninx no dyestuff was found (fig. 5 *D*) unless the perivascular space of the vein had been in connection with the ventricle (fig. 5 *E*). The blood current here is directed outward from the brain, and into the spaces around these veins no dye penetrates, for this would be against the blood stream.

In résumé, the following facts concerning the perivascular spaces were noted:

1. Spaces surround the vessels in the brain of Carassius gibelio.

2. These perivascular spaces are in open communication with the meningeal space and with the ventricle.

3. Particles (of india ink or trypan blue) in colloid suspension in the external or the internal cerebrospinal fluid pass through these communications from the meningeal space or the ventricle into the perivascular spaces.

4. These particles are carried along in the perivascular spaces in the same direction as that in which the blood flows in the vessels.

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9. Charlton, H. H.: Gland-Like Ependymal Structure in the Brain, Proc. Kong. Akad. van Wetenschappen **31**:823, 1928.

From these observations, i. e., that the particles move from the ventricle and the meningeal space through open communications into the perivascular spaces and are carried along in these spaces, one may conclude that the cerebrospinal fluid follows the same course. The vessels in the brain are therefore surrounded with cerebrospinal fluid, which moves in the same direction as the blood in the vessels and which is in direct connection with the external cerebrospinal fluid,

Fig. 2 (fish VII A; section 53, II, 2).—Transverse section (about × 400) through medulla oblongata.

Here, *can* indicates central canal, containing dyestuff; *ms*, meningeal space; *A bas*, basal artery; *a*, branch of basal artery, penetrating the nervous tissue; *c*, carbon particles in the perivascular space, carried along in the same direction as the blood stream (cf. fig. 5 *B* and *C*).

around the brain, and with the internal cerebrospinal fluid, in the ventricle.

Passage of the Cerebrospinal Fluid.—No special apparatus for absorption of cerebrospinal fluid, comparable with the arachnoidal villi of higher animals (Weed[3]), was found here. The absorption

of particles from the internal cerebrospinal fluid in the choroid plexus of the fourth ventricle has already been mentioned. Microscopic examination of the specimens revealed many places where the passage of cerebrospinal fluid from the cerebrospinal cavity might take place.

Cervical Region: The pericerebral space is most pronounced at the level of the first three cervical vertebrae. At the junction of the

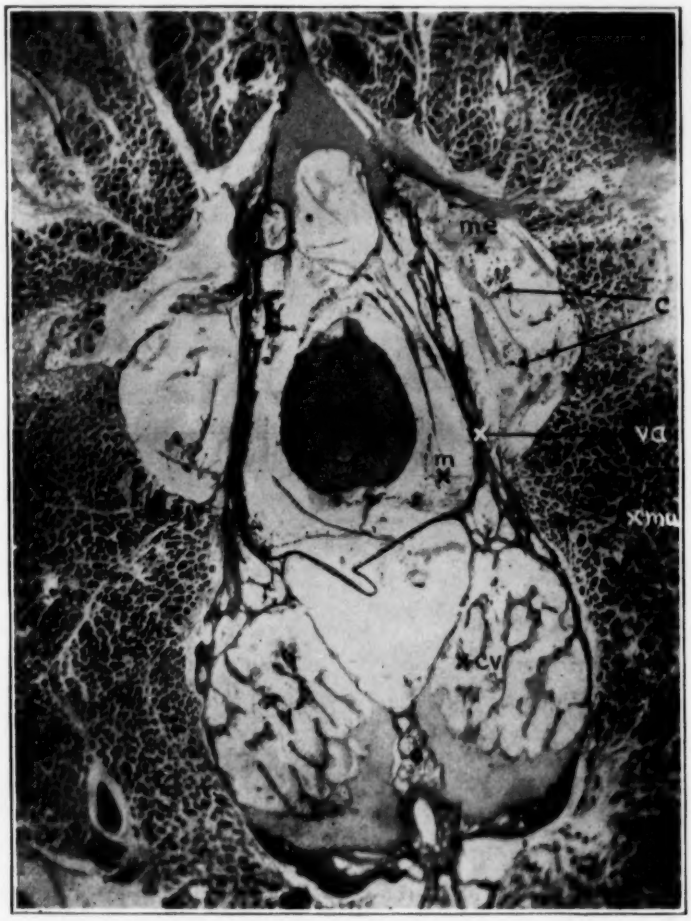

Fig. 3 (fish VII A; section 34, I, 1).—Transverse section (about × 10) through the spinal column at level of the first vertebral arch (cf. fig. 6 *G*).

Here, *va* indicates the vertebral arch; *cv*, the vertebral body; *med*, the cervical portion of the cord; *m*, meningeal tissue; *me*, extravertebral meninx; *mo*, outer layer of the meninx; *mu*, muscle; *c*, accumulations of dye (carbon particles) in the extravertebral continuations of the meningeal space (fig. 6 *B*).

skull and the spine the pericerebral space is laterally no longer enclosed by bone or cartilage; here, there is a wide aperture in the bony case, where the meningeal space is separated from the dorsal musculature only by the thin, pigmented outer layer of the meninx. The first

spinal nerve, here, is composed of a dorsal and a ventral root. The spinal ganglion lies in the meshlike meninx. The outer layer of the meninx has an aperture through which the spinal nerves and blood vessels leave the meningeal space. The meshlike meninx around these nerves and vessels merges with the loose connective tissue, which accompanies them farther.

Somewhat more caudally the spinal cord is surrounded by the first vertebral arch. This arch, however, is too narrow to enclose the whole meningeal space; laterally, part of this space lies outside

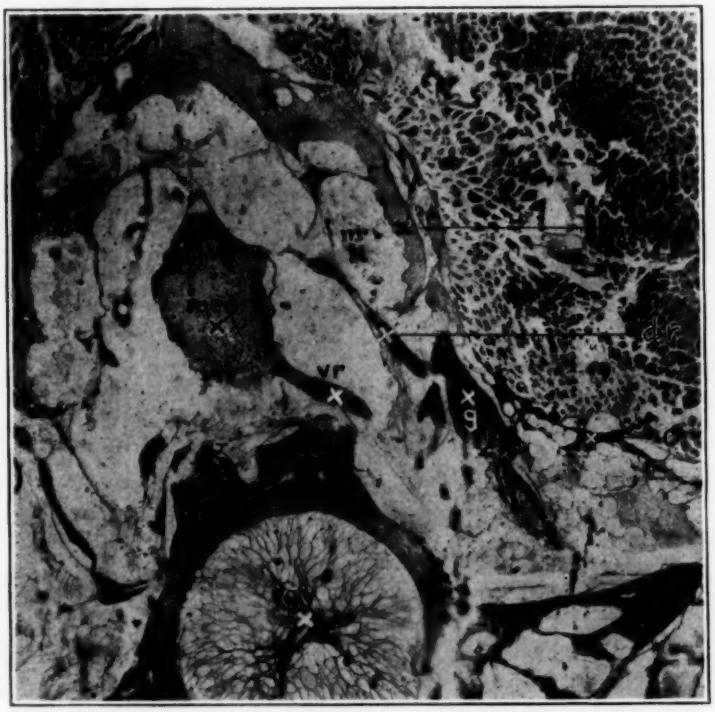

Fig. 4 (fish VII A; section 18, II, 6).—Transverse section (about × 10) through the spinal column at level of the third cervical nerve (cf. fig. 6 *H*).

Here, *va* indicates vertebral arch; *cv*, vertebral body; *med*, cervical portion of cord; *m*, meningeal tissue, containing carbon particles; *dr*, dorsal root of third cervical nerve; *vr*, ventral root of third cervical nerve; *g*, ganglion; *mu*, muscle; *c*, accumulation of dye (carbon particles) in paravertebral connective tissue.

The roots of the third cervical nerve leave the vertebral canal here through an aperture between the vertebral arch and the vertebral body, the foramen intervertebrale. The meshlike meningeal tissue is in contact with the perivertebral connective tissue, but there is no sharp division between them. Dye has been carried from the meningeal space into the connective tissue beside the spinal column.

the arch. This extravertebral continuation of the meningeal space is carried caudally for a distance of several vertebral arches. It is separated from the surrounding muscular and connective tissue by

the outer layer of the meninx (fig. 6*B* and fig. 3). At the ventral side, however, this outer layer disappears, and the extravertebral meningeal tissue is in direct contact with the loose connective tissue, which reaches along the body of the first vertebra ventrally and contains a number of veins. It is not possible to mark exactly the partition between the meninx and the connective tissue. Certainly, it gives the impression that the external cerebrospinal fluid can be carried here into the connective tissue.

Within the first vertebral arch the spinal cord is enclosed in the fibrous shell (see page 525 and fig. 6*F*); somewhat more caudally the cord is again surrounded by the usual meshlike meninx. Close around the cord there is now a pigmented membrane.

Beneath the first vertebral arch the second set of cervical roots arises. The roots join in the extravertebral meninx, where the spinal ganglion also lies. The pigmented membrane which encloses the spinal cord continues around the spinal roots, the ganglia and the nerves. The spinal nerves, accompanied with blood vessels, enter the paravertebral connective tissue. Here, too, no sharp division between meninx and connective tissue can be found; and, again, the passage of the external cerebrospinal fluid into the connective tissue is not improbable. These relations are nearly the same with the next set of cervical roots; but the extravertebral meningeal space becomes smaller here.

At the level of the fourth set of cervical roots, as well as of the following sets, however, no meshlike tissue lies along the spinal column. The spinal ganglion now lies exactly in the intervertebral foramen, thereby practically filling it. The meshlike meninx is not in contact with the loose connective tissue here. It does not seem probable that the cerebrospinal fluid can still pass into the connective tissue here (fig. 6*E*).

The intracranial injections proved that cerebrospinal fluid indeed leaves the cerebrospinal cavity at the places where on microanatomic grounds the passage of cerebrospinal fluid was presumed to take place. Accumulations of dye were found in the extravertebral meninx. The dye had spread from the meningeal space into the perineural and perivascular loose connective tissue, where the outer layer of the meninx lets the spinal nerves and vessels through.

In the specimens in which injections of trypan blue were made the fibers of connective tissue around the first three cervical nerves were colored blue to a considerable distance from the spine. Many histiocytes carrying granules of dye lay in this connective tissue. In many blood vessels in this connective tissue were blue-stained endothelial cells, and sometimes a few cells with a blue protoplasm lay

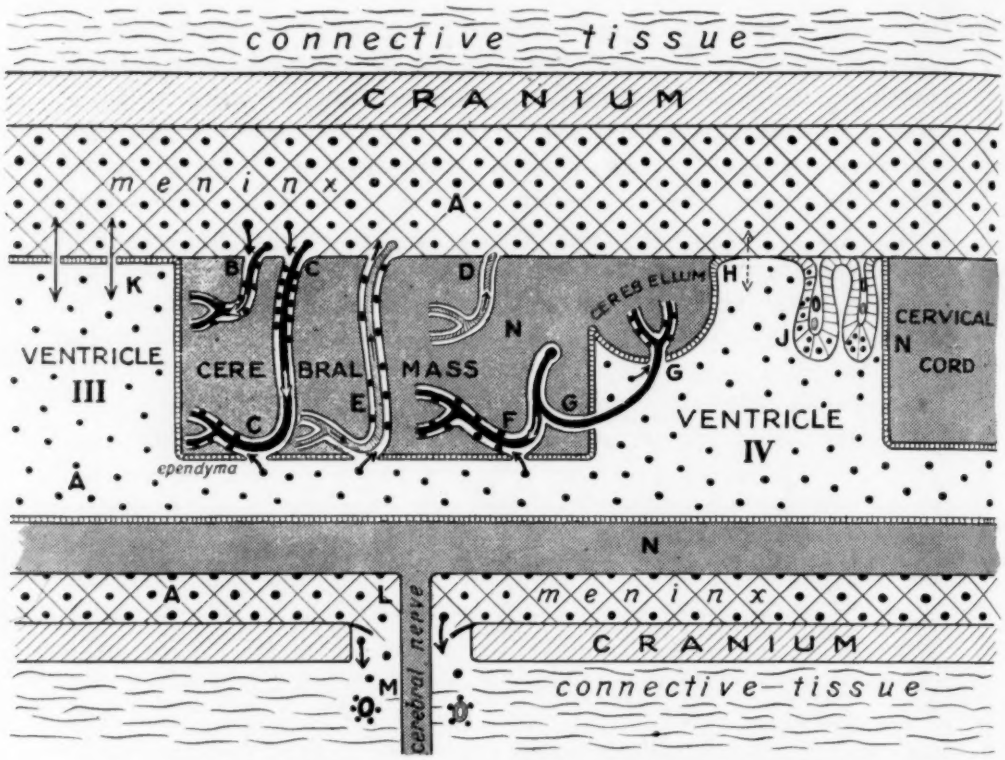

Fig. 5.—This diagram represents a sagittal section through the brain. Arteries are shown in solid black; veins, in hatchure, and dye particles, as dots in india ink.

(*A*) The injected dye spreads through the whole meningeal space and through the ventricles. (*B-F*) The blood vessels in the brain are surrounded by perivascular spaces. (*B*) An artery projects from the meninx into the brain. In its perivascular space dye is carried along in the same direction as the blood stream. (*C*) An artery runs from the surface of the brain to the ventricle. Its perivascular space forms a junction canal between the meningeal space and the ventricle. Dye is carried in the perivascular space in the same direction as the blood stream. A continuous row of particles from the meninx to the ventricle has not yet been formed, and the dye has penetrated only halfway. (*D*) A vein leaves the brain. The space around the vessel opens into the meningeal space. No dye has penetrated here (it would have been against the direction of the blood current!). (*E*) The perivascular space of a vein communicates with the ventricle and later opens into the meningeal space. Dye is transported here right through the brain, from the ventricle to the meningeal space. (*F*) An artery lies just under the ependymal layer. The perivascular space is in open communication with the ventricle. Through this communication dye penetrates into the perivascular space and is carried downstream. (*G*) An arterial branch goes right through the ventricle and enters the cerebellum. Its perivascular space communicates with the ventricle. Dye particles are carried along in the perivascular space and move in the direction of the blood stream. (*H*) In the roof of the fourth ventricle no open foramen exists. The roof, however, is extremely thin; locally, the ependymal layer is interrupted, and the roof consists of meninx only. Probably, possibilities for the exchange of fluid are present here. (*J*) The high epithelium of the choroid plexus of the fourth ventricle contains carbon particles, just where contact with the ventricular fluid is best. At the base of the epithelium lie many blood vessels (in fish III B, containing blue coagulums). There is absorption of colloidal particles from the internal cerebrospinal fluid! (*K*) Through the roof of the third ventricle communication exists between the ventricular fluid and the meningeal fluid (blue lines through the roof between the ependymal cells after injection of trypan blue!). (*L*) A cranial nerve arises from the brain and leaves the cranial cavity through a foramen in the base of the skull. (*M*) Along this nerve the meninx merges with the extracranial connective tissue. Dye escapes from the meninx into the connective tissue and is here transported in adventitial lymph spaces. (*N*) No dyestuff is to be seen in the cerebral parenchyma.

loose in the lumen of the vessel. It was the same with the connective tissue extending from the region ventral to the spinal cord, along the first vertebra, to the extravertebral meninx. The spread of the carbon particles was analogous. These, too, were partly stored in histiocytes, but free particles were frequently noted in the connective tissue, especially immediately around blood vessels, in the adventitial

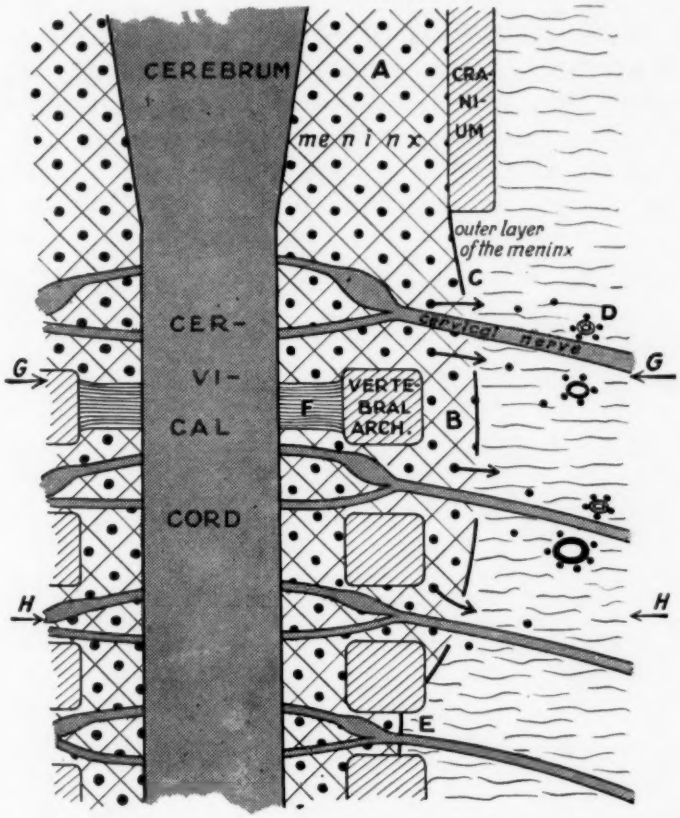

Fig. 6.—This diagram represents the cervical portion of the cord and its surroundings.

(*A*) The meninx contains particles of dye in its meshes. (*B*) Outside the first three vertebral arches lies part of the meningeal space, the arches being too narrow to enclose the whole meningeal space. This extravertebral meninx contains much dyestuff. (*C*) Along the first three cervical nerves the extravertebral meninx merges with the connective tissue. Dye leaves the meningeal space here and enters the connective tissue. (*D*) Dye is transported in adventitial lymph spaces. (*E*) No passage of dye takes place at the level of the fourth cervical nerve. The extravertebral meninx has ended here. (*F*) Inside the first vertebral arch the meningeal space is filled with a stiff fibrous tissue, enclosing the cord as a shell. (*G*) Level of the transverse section shown in figure 3. (*H*) Level of the transverse section shown in figure 4.

lymph spaces. This transportation of dye took place along the first three sets of cervical roots (figs. 4 and 6). More caudally I saw no spread of dye from the meningeal space into the connective tissue (fig. 6 *E*).

Therefore the dye was not only removed from the meningeal space by histiocytes but was also transposed without having been stored in cells (blue fibers of the connective tissue and free carbon particles in the tissue clefts and lymph spaces). This proves that cerebrospinal fluid, too, must have flowed here from the meningeal space into the connective tissue. In the region of the first three cervical nerves, therefore, external cerebrospinal fluid is carried from the cerebrospinal cavity into the surrounding connective tissue.

Cranial Region: In the cranial region, too, several possibilities for the transportation of cerebrospinal fluid were found. Some cerebral nerves leave the skull through wide apertures in which the meshlike meninx and the extracranial connective tissue are in contact with each other. Here, too, one cannot mark a sharp division between them, and here, too, passage of the cerebrospinal fluid seems possible. This is especially noticeable along the olfactory nerves and the optic chiasm.

Indeed, the injected dye evidently spread from the meningeal space into the spongy connective tissue, which, outside the skull, surrounds the cerebral nerves (fig. 5 *L, M*). Hence, the dye was carried through the foramens at the cranial base and was still visible at a considerable distance from the skull, e. g., immediately under the olfactory epithelium. Here, too, the pathways for the transportation of dye lay mainly in the adventitia of the blood vessels. Again, trypan blue was noted in histiocytes and gave a blue hue to the connective tissue; carbon particles were also seen as free corpuscles in the tissue, where they often lay in rows, thereby indicating the course of the tissue clefts and the lymph pathways.

This transportation of dye was distinct along the olfactory nerves and the optic chiasm, but also along the trigeminal nerve I sometimes found undeniable signs of dye escaping from the meningeal space into the extracranial connective tissue. Hence, it is evident that in the cranial region, too, dye was carried from the cerebrospinal cavity at those places where on microanatomic grounds it was assumed that drainage of the cerebrospinal fluid exists, to wit, where the meshlike meninx is in contact with loose connective tissue. The transportation of free dye not stored in cells proves that here, too, the cerebrospinal fluid must have left the meningeal space along the same pathways.

The transportation of external cerebrospinal fluid from the meningeal meshes therefore occurs along the olfactory nerve, the optic chiasm, the trigeminal nerve and in the region of the first three cervical nerves

One may expect that transportation of the dye particles through the tissue clefts and the lymph passages will finally bring them into the blood. Indications that the dye has actually reached the blood

were observed in both fish III B and fish VII A. In fish III B I observed blue endothelial cells in the liver and in fish VII A I noted accumulations of carbon particles in a lymphoid part of the liver and some granules in the interstitial tissue of the kidney.

Cerebrospinal Parenchyma.—Only exceptionally was dyestuff seen in the cerebrospinal parenchyma. In fish III B, blue-stained parenchyma was noted in the olfactory tracts, around the sylvian aqueduct and in the floor of the fourth ventricle. Blue-stained glial fibers were seen here. In the corpora striata of fish VII A carbon particles were observed in the parenchyma just under the ependyma (in symmetric sites to the right and to the left). Generally, however, the parenchyma was not colored, not even near those ventricular, perivascular or meningeal spaces which contained much dyestuff.

That intracranial injection of dye leaves the parenchyma uncolored is a common observation (Goudsmit,[10] Dewey [11]). Hence, between the cerebrospinal parenchyma and the internal, perivascular and external cerebrospinal fluid there also exists a barrier, although it is not an absolute one. Stern's [12] statement that no barrier exists between the cerebrospinal fluid and the parenchyma seems to me inaccurate, at least for the fish used in this study. To my mind, there exists a barrier between the blood and the cerebrospinal fluid (*barrier I*), as well a barrier between the cerebrospinal fluid and the parenchyma (*barrier II*). The blood–cerebrospinal fluid barrier (*I*) lies in the walls of the blood vessels and in the choroid plexus; the cerebrospinal fluid–parenchyma barrier (*II*) lies in the ependyma (with respect to the ventricular fluid), in the membrana limitans gliae perivascularis (with respect to the perivascular cerebrospinal fluid) and in the membrana limitans gliae superficialis (with respect to the external cerebrospinal fluid) (fig. 8).

SCHEMATIC SYNOPSIS

In figures 5 and 6 I have collected the most important of my observations. The facts shown here diagrammatically have been described in the text and are briefly noted in the explanations of the schemas.

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12. Stern, L.: La barrière hémato-encéphalique en physiologie et en clinique, Schweiz. med. Wchnschr. **53**:792, 1923. Stern, L., and Gautier, R.: Recherches sur le liquide céphalorachidien, Arch. internat. de physiol. **17**:138 and 391, 1921; **20**:403, 1923.

COMMENT

My observations prove experimentally that in Carassius gibelio the cerebrospinal fluid in the perivascular spaces flows in the same direction as the blood. This movement of the cerebrospinal fluid must be caused by the pulse wave. Hence, the heart furnishes the driving power for the intracerebral movement of the cerebrospinal fluid. These facts confirm for Carassius gibelio the hypothesis of Sepp and Berkelbach van den Sprenkel, who concluded on theoretic grounds that movement of the cerebrospinal fluid is produced by the pulse wave.

I have not been able to prove the existence of perivascular spaces around the capillaries, and the dye has nowhere penetrated so far. I cannot decide whether the perivascular spaces actually end in the precapillary regions or whether they are still virtually present around the capillaries. Diagrammatically, one can imagine that the movement of perivascular fluid occurs as follows (fig. 7):

The pulse wave in the artery massages the cerebrospinal fluid deeper into the perivascular space. There are three now possible courses for the fluid:

1. The cerebrospinal fluid penetrates into the parenchyma (*A*). This penetration, if present, must be controlled by the cerebrospinal fluid—parenchyma barrier (*barrier II*). At the same time, fluid will leave the parenchyma and enter the perivascular spaces of the venous system (*D*).

2 The cerebrospinal fluid is absorbed into the blood (*B*)

3. If spaces are still virtually present around the capillaries it will be possible for the cerebrospinal fluid to move along the capillaries to the spaces around the venous system (*C-E*).

In my experiments the particles of dye did not penetrate far enough in the perivascular spaces of the small arteries to make it possible to decide which of these three theoretically possible courses actually is followed by the cerebrospinal fluid. My sections prove only that the perivascular cerebrospinal fluid moves in the same direction as the blood in the vessel; hence, I think, the pulse wave must be the driving power for this movement.

That communications between the perivascular spaces and the ventricle were regularly found is essential to the conception of the circulation of cerebrospinal fluid in fishes. In the literature I found no observations on such open communications.

Nowhere did I see perivascular spaces communicating with pericellular spaces, as described by Mott.[13] Moreover, the dye was

13. Mott, F. W.: The Oliver-Sharpey Lectures on Cerebrospinal Fluid, Lancet **2**:1 and 79, 1910.

never observed to reach these pericellular clefts, which I look on as artefacts (Gadrat[14]). In figure 8, finally, the relations between the blood, the cerebrospinal fluid and the cerebrospinal parenchyma are shown as I have conceived them to be in Carassius gibelio, on the basis of the observations described here.

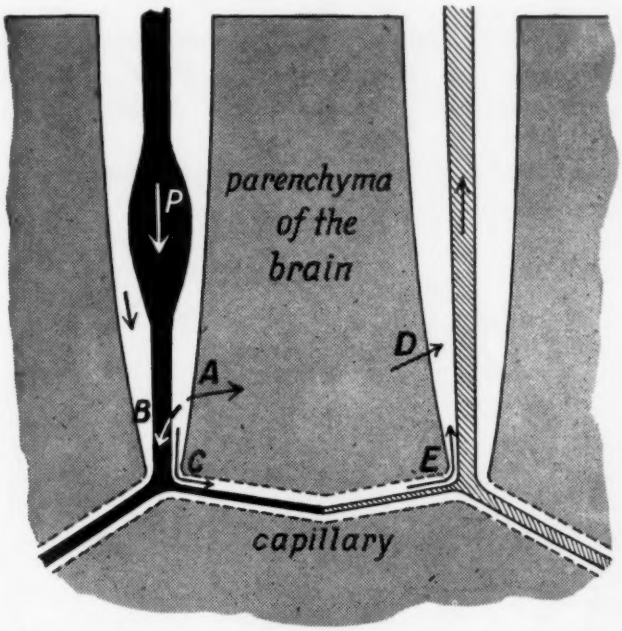

Fig. 7 (partly after Sepp.[2]).—On consideration of what happens to the perivascular cerebrospinal fluid in the precapillary region when it is driven by the pulse wave (*P*) deeper into the periarterial space, three possibilities suggest themselves: 1. The cerebrospinal fluid may leave the periarterial space and enter the parenchyma (*A*). Simultaneously, fluid will leave the parenchyma and flow into the perivenous spaces (*D*). 2. The cerebrospinal fluid may pass through the wall of the vessel (*B*) and be absorbed into the blood. 3. If perivascular spaces are still present around the capillaries, it will also be possible for the cerebrospinal fluid to reach the perivascular spaces of the venous system (*C-E*) by this route.

SUMMARY

From this microscopic study of Carassius gibelio, especially after intracranial injections of dyestuff, the following conclusions may be drawn:

1. Perivascular spaces accompany the blood vessels in the brain.

2. These perivascular spaces are in open communication with the meningeal meshes and with the ventricular space.

3. The perivascular spaces contain cerebrospinal fluid. This perivascular cerebrospinal fluid is in direct communication with the

14. Gadrat, J.: De l'espace périvasculaire du cerveau et de la moëlle, Paris, J. B. Baillière et fils, 1931.

internal cerebrospinal fluid, in the ventricle, and with the external cerebrospinal fluid, in the meningeal spaces.

4. The perivascular cerebrospinal fluid moves in the same direction as the blood stream in the vessels. This movement is caused by the pulse wave.

5. Transventricular arteries are regularly present.

6. The ventricular system contains cerebrospinal fluid (internal cerebrospinal fluid); the brain is surrounded with cerebrospinal fluid (external cerebrospinal fluid), lying in the meshes and chambers of the meningeal tissue.

7. An extensive exchange of fluid occurs between the internal and the external cerebrospinal fluid, as shown by the rapid spread

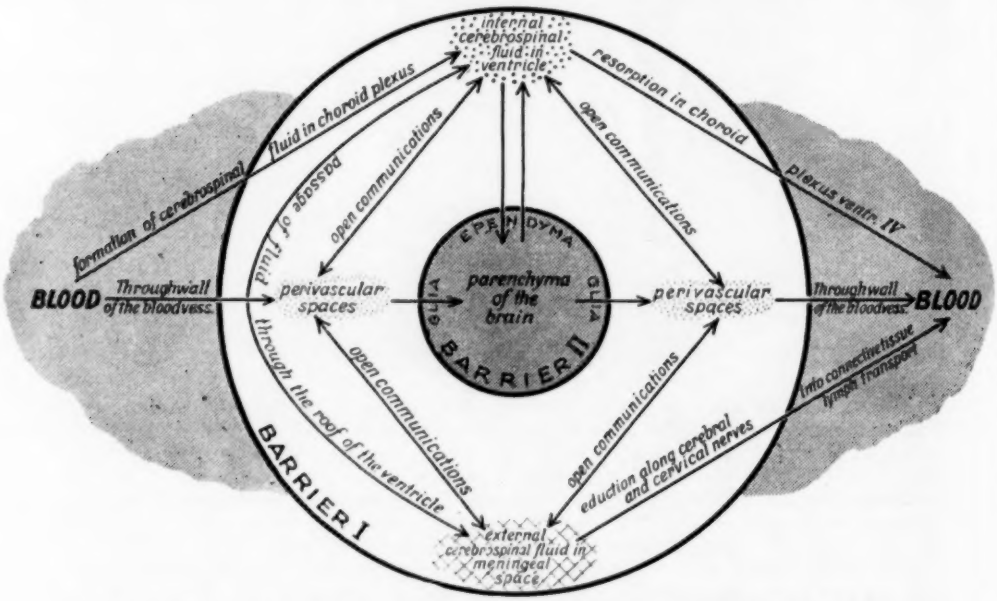

Fig. 8.—Probable relations of the blood, the cerebrospinal fluid and the cerebrospinal parenchyma in Carassius gibelio.

It is to be noted (1) that there is always cerebrospinal fluid between the blood and the parenchyma; (2) that selective barriers separate the cerebrospinal fluid from the blood and the parenchyma from the cerebrospinal fluid, and (3) that ventricles, meningeal space and perivascular spaces form one communicating system, containing the cerebrospinal fluid.

through both of dye injected into the pericerebral spaces. This exchange of fluids occurs (*a*) through the thin roof of the third ventricle and (*b*) through the perivascular spaces of vessels reaching the surface of the brain from the ventricle.

8. The roof of the fourth ventricle has no open foramen. This roof is locally extremely thin; in some places there is no ependyma, and the roof consists of meninx only.

9. The choroid plexus of the fourth ventricle absorbs colloidally suspended particles from the internal cerebrospinal fluid.

10. Interepithelial capillaries occur in the choroid plexus of the third ventricle, in the pineal tube and in the roof of the third ventricle.

11. Transitions between meninx and connective tissue occur along the olfactory nerves, the optic chiasm, the trigeminal nerves and the first three cervical nerves.

12. At these points the external cerebrospinal fluid drains into the connective tissue.

13. With respect to trypan blue there exist a blood–cerebrospinal fluid barrier and a less absolute cerebrospinal fluid–parenchyma barrier. With respect to india ink the second barrier is the stronger.

Laboratory of Pathology, Oostersingel 63.

ELECTRICAL RESISTANCE OF THE SKIN

Effect of Size of Electrodes, Exercise and Cutaneous Hydration

IRVIN H. BLANK, Ph.D.
AND
JACOB E. FINESINGER, M.D.
BOSTON

VARIOUS factors influencing the measurement of skin resistance have been repeatedly investigated. Various types of apparatus, electrodes and electrode pastes have been used in these investigations. Variations in skin resistance have often been observed which were not entirely understood. We have felt that by a better understanding of the variations in the technic of measuring skin resistance more consistent and comparable results could be obtained. The use of a standardized technic by different investigators would be helpful.

Several years ago we built an apparatus for measuring the galvanic skin response (psychogalvanic reflex). This apparatus made use of a Wheatstone bridge circuit, in which a pulsating, direct current of constant amperage flowed continuously through a subject who was connected into one of the arms of the bridge. Not long after we started to use this apparatus for investigating the galvanic skin response to auditory stimuli it was observed that it was sometimes difficult to obtain a constant resistance to be used as a base line from which the effect of a stimulus could be measured. As a rule the resistance dropped during the first twenty to thirty minutes, but it did not always drop the same amount. Other investigators[1] have also observed this drop. In addition, the apparent, or measured, resistance of the same area of skin on the same subject varied from day to day. It was not always possible to obtain a constant resistance even when all external stimuli were held at a minimum. What factors other than psychic stimuli were responsible for these changes in skin resistance?

A review of the literature and discussion of the problem with several investigators working in this field did not yield specific information as to the causes of change in apparent resistance other than psychic stimuli.

From the Departments of Dermatology and Neuropsychiatry, Harvard Medical School, and the Departments of Dermatology and Psychiatry, Massachusetts General Hospital.

1. Thouless, R. H.: The Technique of Experimentation on the Psychogalvanic Reflex Phenomenon and the Phenomenon of Tarchanoff, Brit. J. Psychol. **20**:219-240 and 309-321, 1930.

Landis and DeWick [2] published a review of the entire field in 1929, which was extensively expanded by Landis in 1932.[3] Many reports by other investigators have appeared since then; the papers applying directly to the factors we are investigating will be cited in the context of the paper.

Our early work on this problem led us to believe that such factors as (*a*) variations in the size of the electrode, (*b*) the amount of activity previous to the measurement of the apparent resistance and (*c*) the hydration of the skin by the electrode paste had not been given sufficient consideration by many of the workers in this field. The results of the investigations of these three factors are reported in this paper.

APPARATUS

A simple apparatus was constructed for us by Dr. M. A. Wenger, making use of the Levine circuit.[4] The apparatus (fig. 1) consists of two 4.5 volt dry cells connected in series, two Centralab variable resistances of 50 and 750 ohms maximum resistance connected as a potential divider, a Triplet D.C. voltmeter no. 677 and a Triplet D.C. microammeter no. 676. The entire apparatus was assembled at a cost of less than $25. Since the smallest scale division of the microammeter is 1 microampere, this instrument is not very accurate when one is working with extremely small currents. Up to the present we have been interested in large changes and have found this instrument sufficiently accurate for our needs.

FACTORS AFFECTING RESISTANCE OF SKIN

Size of Electrode.—With any type of electrode the junction between the metallic element and the subject is always made with an aqueous solution of an electrolyte. Under some conditions this solution may be only the normal sweat on the skin. Inert nonelectrolytes, such as kaolin or agar, may be added to give a semisolid or gel consistency to the electrolyte solution. Some investigators have discussed the effect of the size of the electrode on the apparent resistance.

If the metallic element of the electrode is carefully placed on the skin, with only a film of the electrolyte solution between the metal and the skin, the area of the metallic element and the area of the skin wet with the solution are approximately equal. With certain types of electrodes, however, the metallic element may be at some distance from the skin, and the area of the metallic element may differ appreciably from

2. Landis, C., and DeWick, H. N.: The Electrical Phenomena of the Skin (Psychogalvanic Reflex), Psychol. Bull. **26**:64-119, 1929.

3. Landis, C.: Electrical Phenomena of the Skin (Galvanic Skin Response), Psychol. Bull. **29**:693-752, 1932.

4. Levine, M.: Measurement of Electrical Skin Resistance, Arch. Neurol. & Psychiat. **29**:828-842 (April) 1933.

the area of the skin wet with the solution. Under such conditions, how is the size of the electrode to be determined? If the area of skin wet with the electrolyte solution changes during the experiment as a result of evaporation of water from the electrode paste, how will this affect the apparent resistance of the skin? To answer these questions, the following investigations were carried out.

A Lucite cup electrode[5] (fig. 2), described in the following paragraph, was selected because it may be readily constructed in a variety of sizes, and the size of the metallic element within the Lucite cup may be varied independently of the size of the cup. The electrode paste is confined to a definite area of the skin, and evaporation of water from the paste is prevented. In addition, the electrode can be easily and quickly applied and removed from the cutaneous surface.

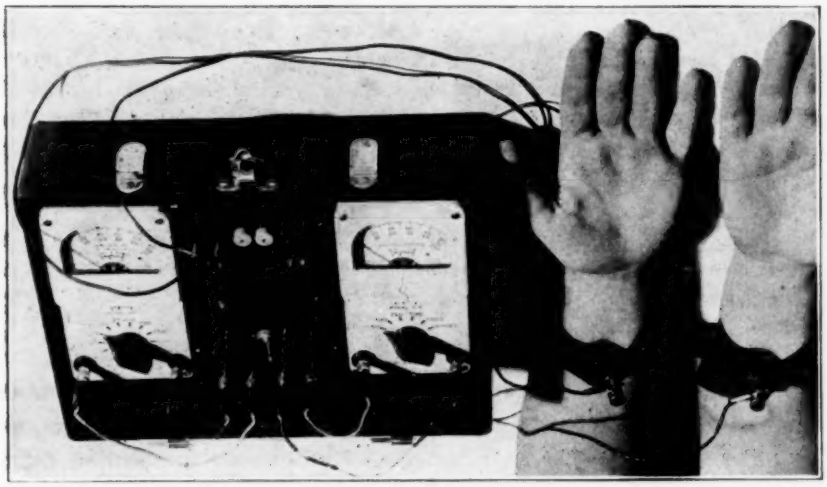

Fig. 1.—Apparatus for measurement of electrical skin resistance.

The metallic element in this electrode is a thin (0.5 mm.) zinc disk. The electrolyte solution is 1 per cent zinc sulfate made into a paste with 5 per cent agar. The electrode is constructed so that the zinc disk is in contact with the base of the shallow Lucite cup, 5 mm. in depth. The disk has the same diameter as the cup, allowing only enough clearance so that it may be removed for cleaning. The cup is filled with the zinc sulfate-agar paste. The electrode is held in place on the skin by means of a strip of sheet rubber around the hand or arm. These electrodes may be quickly and easily applied to an extremity and held firmly in place with a minimum of discomfort to the subject.

Pairs of electrodes whose cups and disks were 1, 2 and 4 cm. in diameter were constructed. The subject was lying down at rest during the entire experiment. Since it was desired to minimize the changes in resistance due to sweating, the volar surface of the forearm, which has fewer and less active sweat

5. Designed by Dr. M. A. Wenger and manufactured by Forest Products, Inc., 739 Boylston Street, Boston.

glands than the palms, was chosen for this study. The skin of the volar surface of the forearm is anatomically similar to the skin of the dorsum of the hand, an area frequently used by other investigators.

A 2 cm. electrode was placed on the midvolar surface of each forearm, and the apparent resistance was measured at a potential of 1 volt, the current being allowed to flow through the subject for not longer than three seconds. The electrodes were removed immediately after the reading was made; in this way the electrodes did not stay on the skin longer than one minute. This technic was used

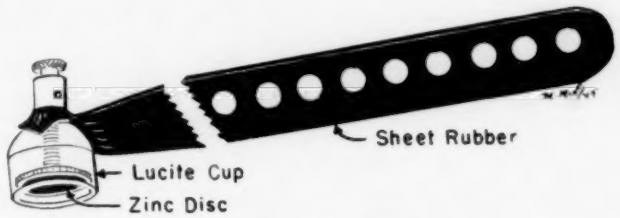

Fig. 2.—Lucite cup electrode.

in order that any changes in the skin due to the flow of current or hydration of the skin might be minimized. Although one cannot be sure that no such changes occur in the skin, even when the current is allowed to flow for only a short time or when contact of the electrode with the skin is of short duration, evidence is available that if such changes do occur they are nearly reversible, and hence the four minute period allowed to elapse before the electrodes are again applied to the skin is ample time for recovery to take place.

For this experiment, measurements were made on the same area of skin every five minutes, until three or four successive measurements gave similar results. When the readings became constant, the subject was judged to be

TABLE 1.—*Effect of Size of Electrode on Apparent Skin Resistance* *

Size of Electrode		Apparent Resistance, in Ohms × 10^{-3} for Six Subjects					
Diameter, Cm.	Area, $Cm.^2$	1	2	3	4	5	6
1.0	0.79	3,750	4,280	5,000	6,000	6,000	25,000
2.0	3.14	1,430	1,760	3,330	2,500	2,500	8.330
4.0	12.56	517	400	698	545	980	2,940

* Voltage was 1.0.

sufficiently rested, so that any previous activity he may have had no longer affected the skin resistance. This point was reached about thirty minutes after the subject lay down. After the thirty minute rest period a new area of the volar surface of each forearm closer to the antecubital space was chosen, and similar successive readings were made with pairs of electrodes which were 1, 2 and 4 cm. in diameter. The apparent resistances determined for an experiment of this type on 6 subjects, in which the three sizes of electrodes were used, are shown in table 1. It is clearly seen in the values for each subject that the apparent resistance decreases as the size of the electrode increases.

If, in the circuit being investigated, the body of the subject conducted electricity in the same way as does an electrolyte solution, the current density (microamperes per square centimeters) would be constant and independent of the size of the electrode. In table 2, which shows the same data as table 1 calculated as current densities, it is seen that the current density is not constant when the size of the electrode changes. The greatest divergence occurs for the 1 cm. electrodes. This

TABLE 2.—*Variations in the Current Density* as the Size of the Electrode Is Varied*

Size of Electrode		Current Density for Six Subjects					
Diameter, Cm.	Area, Cm.^{2}	1	2	3	4	5	6
1.0	0.79	1.01	0.89	0.77	0.63	0.64	0.25
2.0	3.14	0.69	0.54	0.39	0.38	0.38	0.19
4.0	12.56	0.46	0.60	0.34	0.44	0.26	0.14

* Current density is expressed in microamperes per square centimeter.

may be due to the lack of refinement in technic, or it may indicate the difference of the conductance of the body as compared with the conductance of an electrolyte solution. Nonuniformity of the skin no doubt affects these measurements.

When using other types of electrodes, we had the impression that the size of the metallic element could be varied appreciably without changing the apparent skin resistance as long as the area of skin wet with the electrolyte solution was held constant. The present type of electrode offered a good opportunity for studying this impression more

TABLE 3.—*Effect of Changing the Size of the Metallic Disk Only on Apparent Skin Resistance**

Area of Lucite Cup, Cm.^{2}	Area of Metallic Disk, Cm.^{2}	Apparent Resistance, in Ohms × 10^{-3} for Six Subjects					
		1	2	3	4	5	6
12.56	12.56	833	517	400	3,070	6,230	.....
12.56	3.14	833	483	309	3,330	6,230	1,430
12.56	0.79	833	517	219	3,070	5,550	1,210

* Voltage was 1.0.

carefully. Measurements were made on the volar surface of the forearm of 6 subjects at rest for at least thirty minutes. The 4 cm. cup was used with the 1, 2 and 4 cm. zinc disks. Table 3 shows that the apparent skin resistance remained nearly constant if the area of skin wet with the electrolyte solution was constant, even when the area of the metallic element varied sixteenfold. The area of skin wet with the electrolyte solution will be called the "effective electrode."

The foregoing data indicate that care should be used in applying electrodes to the surface of the skin. If an area of the skin larger than the area of the electrode is accidentally wet with the electrolyte solution, the apparent skin resistance will be low; and as the wet area outside the electrode dries the apparent skin resistance will increase. This is specifically demonstrated in the following experiment.

Two sets of electrodes, each 2 cm. in diameter, were applied to the volar surfaces of the forearms and allowed to remain on the skin continuously for the duration of the experiment. Measurements of resistance were made at a potential of 1 volt every five minutes until the resistances became constant. At this time an area about 1 cm. wide outside each of two electrodes was wet by swabbing with a 1 per cent solution of zinc sulfate. The skin outside the other two electrodes was not wet with the solution.

The apparent resistance immediately decreased for the set of electrodes around which the skin was swabbed but as the skin spontaneously dried the apparent resistance gradually returned to almost the same value as that previous to swabbing. The apparent resistance remained constant for the unswabbed areas. Figure 3 also shows that the return after swabbing was hastened if the evaporation was speeded up by blowing the swabbed areas with air. Liu and Wu [6] referred to a decrease in resistance when they wet their electrodes with saline solution.

Thus it is clearly seen that the apparent resistance decreases as the size of the electrode is increased and that the size of the effective electrode is determined not by the size of the electrode itself, or of the metallic part of the electrode, but by the area of skin wet with the electrolyte solution. Although many investigators have pointed out the necessity of preventing evaporation from the electrode paste in order to avoid changes in the concentration of the paste, we believe that a greater artefact is due to changes in size of the effective electrode as evaporation occurs. Water or aqueous solutions are often used for cleansing the skin before the electrodes are applied, and subsequent evaporation of these solutions outside the area covered by the electrode changes the size of the effective electrode. The results of the experiment just described suggest that the changes in apparent resistance observed during profuse sweating, as in cases of hyperhidrosis, may be due to an increase in the size of the effective electrode when continuity is established between the electrode paste and the film of sweat outside the limits of the electrode. For an actively sweating palm the size of the effective electrode would be difficult to determine. In describing a technic for measuring skin resistance, the actual area of skin wet with the electrode solution should be stated, and this area should be held as nearly constant as possible for the duration of the experiment.

6. Liu, S. C., and Wu, H.: A Method for Measuring the True Electrical Resistance of the Skin, with Some Observations, Chinese J. Physiol. **6**:63-70, 1932.

Exercise.—Since measurements of skin resistance are frequently made on ambulatory subjects, the amount of activity just previous to the time when the resistance is measured will vary. Reports of these measurements do not always indicate the extent of this activity, such as walking or climbing stairs, and often do not state whether or not the subject was asked to rest before the measurement was made. During rest following exercise, there probably will be an increase in apparent resistance, possibly associated with decrease in sweating [7] and relaxation of muscular tension.[8] The following experiment has been chosen, from

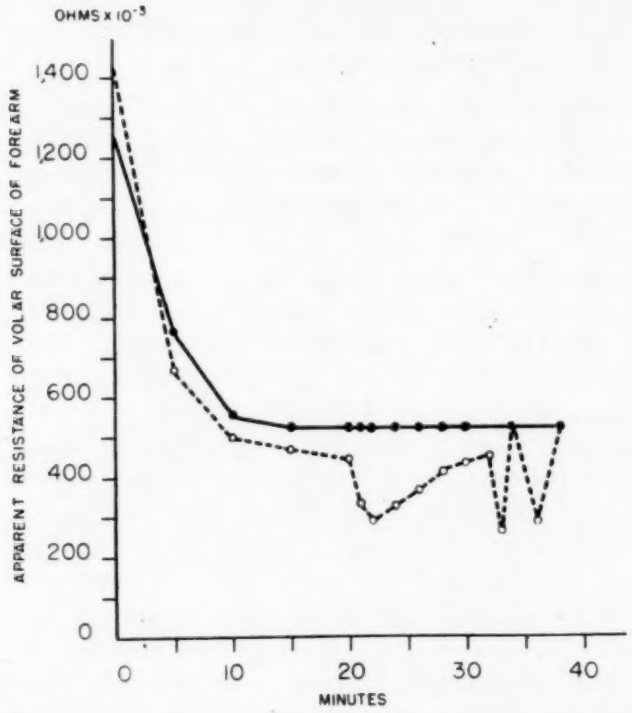

Fig. 3.—Effect on the apparent resistance of the skin of increasing the size of the effective electrodes by swabbing the skin around the electrodes.

The solid line shows readings for the control electrodes; the broken line, readings for the electrodes around which the skin was swabbed with 1 per cent aqueous solution of zinc sulfate, at twenty, thirty-two and thirty-four minutes. Drying occurred spontaneously after the first swabbing; the area was blown with air after the second and third swabbings.

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7. Richter, C. P.: Physiological Factors Involved in the Electrical Resistance of the Skin, Am. J. Physiol. **88**:596-615, 1929.

8. White, M. M.: Relation of Bodily Tension to Electrical Resistance, J. Exper. Psychol. **13**:267-277, 1930. Wenger, M. A.: A Study of Physiological Factors: The Autonomic Nervous System and the Skeletal Musculature, Human Biol. **14**:69-84, 1942.

many similar tests we have made, to show the rise and fall of apparent resistance during rest and exercise.

A subject who had been walking a little just previous to the experiment was asked to lie down. Lucite electrodes were immediately applied to the midvolar surfaces of both forearms and to both palms and were allowed to remain in place for the entire experiment. Single measurements of skin resistance at a potential of 1 volt were made on the forearms and the palms at five-minute intervals. For each measurement the current was allowed to flow for less than three seconds. After twenty minutes the successive measurements became relatively constant, indicating that the effect of any previous exercise had disappeared. After thirty minutes the subject was asked to stand up and start exercising by stepping up

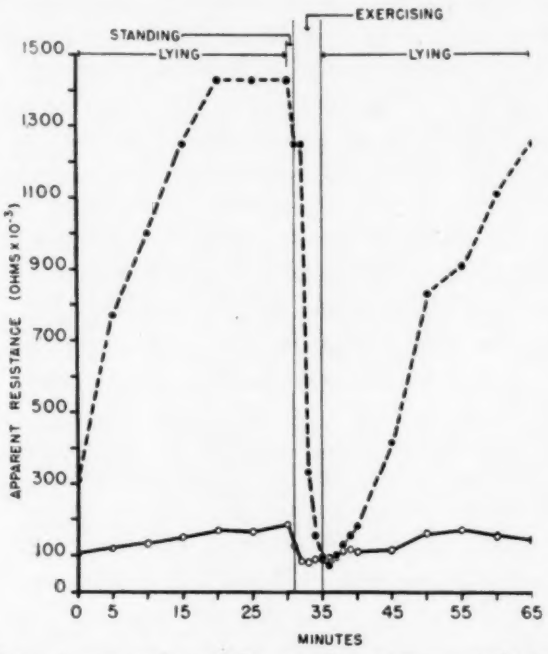

Fig. 4.—Effect of rest and exercise on the apparent resistance of the skin. The solid line indicates readings for the palms; the broken line, readings for the volar surfaces of the forearms.

and down on a 12 inch (30 cm.) step at the rate of sixteen times per minute. This was continued for four minutes, measurements of resistance being made every minute. The subject again lay down, and measurements of resistance were continued every five minutes for thirty minutes. The results of this experiment are shown in figure 4.

During the first twenty minutes the apparent resistance of both the forearms and the palms rises. We believe that the change in apparent resistance during the first rest period is the resultant of at least two factors: the rise in resistance resulting from resting and a decrease in resistance associated with hydration of the stratum corneum by the electrode paste. The latter factor will be discussed in the succeeding section of this paper.

The apparent resistance of the volar surface rises fairly uniformly. This probably indicates that the sweat glands of this surface steadily decrease their rate of functioning. The lower apparent resistance of the palms as compared with that of the volar surfaces at the end of the rest period probably indicates that during rest the sweat glands of the palms are more active than the sweat glands of the forearms. As the subject begins to exercise, the palmar resistance quickly drops to a minimum, at about which level it remains during continued exercise. The resistance of the skin of the forearm drops more slowly but reaches approximately the same level. We feel that this low level of resistance of both the palms and the volar surfaces of the forearms represents the resistance of these areas of skin at a time when the sweat glands are actively functioning. It is interesting that at this time the apparent resistance of the palms and that of the surfaces of the forearms are of the same magnitude. During the rest period following exercise the rise in apparent resistance, which accompanies resting, with its diminished activity of the sweat glands, is again seen.

This experiment indicates that a subject for measurements of skin resistance should have a rest period before the measurements are made in order to minimize the effects of his previous activities.

Hydration of the Skin.—In a study of some of the factors associated with the measurement of skin resistance, Levine [4] stated:

> . . . One might expect that the paste, soaking the skin, might lower its resistance, or that the paste might provide stimuli which could produce changes. But again the fact that after long periods of contact with the paste, the resistance may, in different patients, remain the same, may increase or may decrease, offers strong evidence against the idea that the paste itself can change skin resistance.

We, too, have observed that during the first half-hour the electrodes are on the skin the apparent resistance may sometimes decrease, sometimes increase or sometimes remain nearly constant. These variations, which may be large or small, may occur in the same subject when measurements are being made at different times or may be observed on two subjects measured at the same time. We have not felt, however, that these observations justified the conclusion drawn by Levine that this is "strong evidence against the idea that the paste itself can change skin resistance." The electrode paste might be acting on the skin so as always to change the apparent skin resistance in one direction. If at the same time another factor were acting to change the skin resistance in the opposite direction, the resultant change in resistance would be the sum of the changes caused by the two factors, and the resultant change might be in either direction, depending on which factor was the greater.

We believe that this is actually what was happening in the experiments of Levine, and what happens when many types of electrodes are used. In the previous section of this paper it was shown that the

apparent skin resistance increases during a period of rest following exercise. We believe that the electrode paste causes hydration of the outermost layer of the skin, which results in a decrease in apparent skin resistance. Ebbecke [9] has referred to this drop in resistance which accompanies hydration of the skin. If the changes due to resting and to hydration occur simultaneously, the resultant change is the algebraic sum of these two factors and may be either an increase or a decrease, depending on which factor is the greater. The following experiments were devised to test this hypothesis and to evaluate the factors of exercise and hydration.

Subjects were asked to lie down at the beginning of the experiment and remained lying down with their arms in the same position throughout the experiment. Two of the cup electrodes 2 cm. in diameter, filled with a 1 per cent zinc sulfate–agar jelly, as previously described, were placed on the volar surface of each forearm near the antecubital space. These electrodes were allowed to remain in position on each forearm in contact with the skin throughout the whole experiment, which lasted about one hour. Another set of similar electrodes was placed on the forearms about 3 cm. below the first set. During the first part of the experiment the second set of electrodes was allowed to remain on the skin each time only long enough to obtain a reading and then removed. The time required to obtain a reading was from thirty to sixty seconds, and the actual time during which current flowed through the skin was less than three seconds. A potential of 4 volts was used, and readings were made at five minute intervals. After each reading the electrodes were removed, and the areas of skin in contact with the electrodes were gently wiped with gauze. After the apparent resistance became constant, i. e., when three consecutive readings were the same, it was judged that the factor of exercise, or, more correctly, that of rest following exercise, was no longer causing the apparent skin resistance to change. At this point the electrodes were placed on the same areas of the skin and from this time on were not removed after each reading.

Figure 5 shows the changes which occurred in similar experiments on 2 subjects. The solid line in each graph indicates changes as measured with the electrodes which remained in place continuously throughout the whole experiment. The dotted line in each graph represents the changes as measured with electrodes which were removed after each reading for the first thirty minutes and then allowed to remain continuously on the skin for the second thirty minutes. We believe that when the electrodes were removed the changes in resistance were due primarily to the rest following exercise. When the electrodes subsequently remained in place, the changes were due primarily to the hydration of the skin by the electrode paste. As shown in figure 5 *A*, the hydration caused a drop in apparent skin resistance which was greater than the rise which occurred during resting. Thus there resulted a net

9. Ebbecke, U.: Die lokale galvanische Reaktion der Haut, Arch. f. d. ges. Physiol. **190**:230-269, 1921.

decrease in apparent skin resistance. In figure 5 *B* the drop caused by the hydration is less than the rise caused by resting, and hence there is a net increase in the apparent resistance. The results for these 2 experiments are shown because for 1 of the subjects the apparent resistance rose and for the other the resistance fell during similar determinations. This is the situation mentioned by Levine.

The skin is a complex organ, anatomically and physiologically. When a 1 per cent zinc sulfate–agar jelly is placed on the skin, many changes

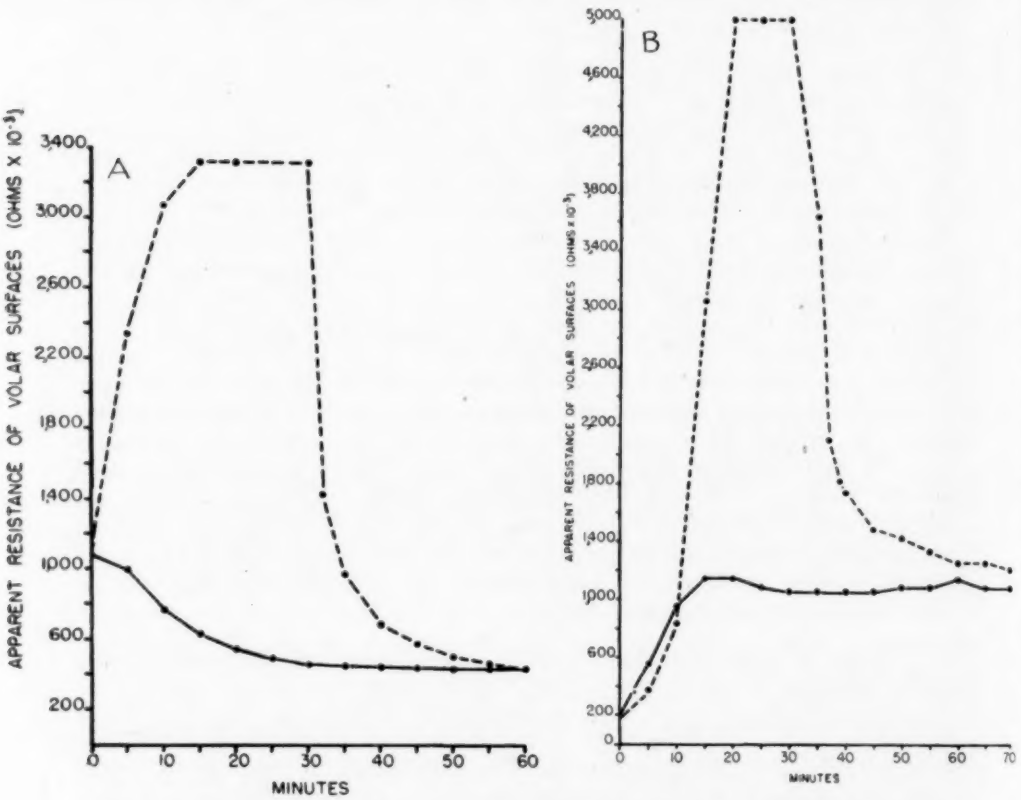

Fig. 5.—Effect on the apparent resistance of the skin of removing electrodes between readings. The broken line indicates readings for the first set of electrodes, removed between readings for thirty minutes and then left on the skin continuously; the solid line, readings for the second set of electrodes, left on the skin continuously. The graphs are for 2 subjects, *A* and *B*.

may occur which might cause a drop in skin resistance. It is our opinion that one of the most probable mechanisms producing this change is the hydration of the outermost layer of the skin, the stratum corneum. Most of the tissues of the body are relatively good conductors of electricity. The skin, on the other hand, is a poor conductor; i. e., it has a high resistance. The seat of this high resistance is probably the outer layer

or layers of the skin, since the resistance can be greatly reduced by the most superficial abrasion or puncture.[10] The stratum corneum is thought to contain less than 20 per cent water, as compared with the deeper layers of skin and other body tissues, which contain from 75 to 80 per cent water.[11] The cells of the stratum corneum have lost their water during the normal process of keratinization. These cells, however, relatively easily take up water again, i. e., become hydrated. On hydration the stratum corneum might be expected to become a better conductor, since electrolytes are already present in this tissue. If this hypothesis is correct, the skin when covered with a gauze compress soaked with distilled water should show a drop in resistance similar to that occurring when it is covered with an electrode of the type previously described. Also, the resistance should again rise when the skin is allowed to dry out by removing the electrodes from a hydrated area. The results of the following experiment, as shown in figure 6, support this hypothesis.

Two sets of electrodes were placed on the forearms, as in the previous experiment. During the first thirty minutes of rest each set remained on the skin only long enough to obtain one measurement every five minutes. After thirty minutes one set of electrodes was placed on the skin and allowed to remain in place, and the current was allowed to flow through the skin for only three seconds each time the resistance was measured. The other areas of skin the resistance of which had been measured were covered with gauze compresses wet with distilled water. The area of each compress was the same as that of the electrodes. These remained on the skin for fifteen minutes. At the end of this time the compresses were removed, the areas gently but thoroughly dried with gauze and the electrodes immediately placed on the skin and allowed to remain in contact with the skin for fifteen minutes. After fifteen minutes the electrodes were again removed and during the succeeding twenty minutes were placed on the skin only long enough to make a measurement of resistance once every five minutes.

In figure 6 it is seen that the area to which no compress was applied shows a change in apparent resistance quite similar to that illustrated by the broken lines in figure 5. It is also seen that the areas wet with distilled water alone, as illustrated by the solid line in figure 6, show a decrease in apparent resistance during the fifteen minute period of application of compresses approximately equal to the decrease in apparent resistance which occurs when the electrodes are held continuously to the skin.

10. Richter, C. P.: The Significance of Changes in the Electrical Resistance of the Body During Sleep, Proc. Nat. Acad. Sc. **12**:214-222, 1926. Lewis, T., and Zotterman, Y.: Vascular Reactions of the Skin to Injury: VIII. The Resistance of Human Skin to Constant Currents in Relation to Injury and Vascular Response, J. Physiol. **62**:280-288, 1927. Densham, H. B., and Wells, H. M.: The Mechanism by Which the Electrical Resistance of the Skin Is Altered, Quart. J. Exper. Physiol. **18**:175-184, 1927.

11. Rothman, S., and Schaaff, F., in Jadassohn, J.: Handbuch der Haut- und Geschlechtskrankheiten, Berlin, Julius Springer, 1929, pp. 167-171 and 275-278.

When the electrodes are removed from the skin, the apparent resistance again increases, a change which we feel is due to drying out of the stratum corneum.

These experiments show that the apparent resistance drops as a result of contact of water or aqueous solutions with the skin and that this decrease is caused by hydration resulting from contact of the electrode paste with the skin. In experiments which measure the effect of various stimuli on apparent resistance, it would be best to allow this

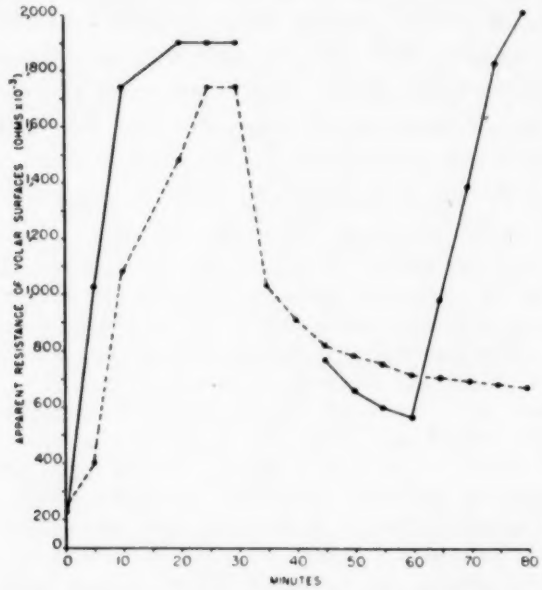

Fig. 6.—Effect on the apparent resistance of the skin of application to the skin of compresses wet with distilled water. The broken line indicates readings for the first set of electrodes, removed between readings for thirty minutes and then left on the skin continuously for fifty minutes. The solid line represents readings for the second set of electrodes. These electrodes were removed between readings for thirty minutues; compresses were applied for fifteen minutes, and electrodes were left continuously on the skin for fifteen minutes and then removed between readings during the final twenty minutes.

hydration to occur and the apparent resistance to become constant before attempting to measure the effect of the stimuli.

SUMMARY

The following observations were made: 1. Apparent skin resistance decreases (*a*) as the size of the electrode is increased and (*b*) as the superficial layer or layers of skin become hydrated as a result of continuous contact of electrode paste with the skin. 2. Apparent skin resistance increases during rest following exercise or activity. 3. The size of the electrode is determined by the area of skin wet with the

electrode paste or sweat (effective electrode), and not by the absolute size of any part of the electrode itself. 4. Any aqueous film, such as sweat, outside the area of the electrode, but continuous with the electrode paste, acts to increase the size of the effective electrode. 5. The values for apparent resistance of two areas of skin, such as the palmar and the volar surface of the forearms, which may differ greatly when the subject is at rest, approach the same magnitude when the patient exercises vigorously.

In any experiment in which the effect of a stimulus on apparent skin resistance is being measured one should be sure that the resistance is not changing as a result of (*a*) variation in the area of skin wet with the electrode paste or with sweat, (*b*) rest following exercise or (*c*) hydration of the skin by the electrode paste.

NEUROLOGIC DISEASE FOLLOWING INFECTIONS OF THROAT AND SKIN AND INCIDENCE OF DIPHTHERITIC INFECTIONS

CAPTAIN LEWIS H. BRONSON
MEDICAL CORPS, ARMY OF THE UNITED STATES

A NEUROLOGIC syndrome apparently infectious in origin has been reported among the members of the armed forces of the United States in the recent war. These patients have shown varying degrees of neurologic disturbance, ranging from mild peripheral neuritis to severe debility involving the central nervous system as well as the peripheral nerves, similar to the Guillain-Barré syndrome.[1] The great majority of these patients had, or had previously had, cutaneous disease. Those with no history of cutaneous disease gave a history of a severe sore throat during the period of approximately one month prior to the onset of neurologic symptoms.

It has been assumed by some investigators[2] that the disorder in these patients was the result of infection with Corynebacterium diphtheriae. In support of this view, virulent diphtheria organisms have been isolated from the throat, nose and lesions of the skin of some of the patients. In the majority of instances, however, cultures have failed to show C. diphtheriae. It is, of course, known that the earlier in the disease a culture is obtained, the greater is the likelihood of a positive culture for C. diphtheriae if that is the organism concerned. There is some evidence, also, that diphtheria organisms may lose their virulence while still present in the human body. It is not the purpose of this paper to prove or disprove the theory that neurologic syndromes following cutaneous disease are the result of exposure to the toxin of the diphtheria bacillus. In all likelihood some are of diphtheritic origin. There is, however, considerable reason to doubt that C. diphtheriae is the sole etiologic agent, and the results of certain studies will be offered which seem to support the possibility that other factors may be concerned.

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1. Roseman, E., and Aring, C. D.: Infectious Polyneuritis: Infectious Neuronitis, Acute Polyneuritis with Facial Diplegia, Guillain-Barré Syndrome, Landry's Paralysis, etc., Medicine **20**:463, 1941.

2. Liebow, A. A.; MacLean, P. D.; Bumstead, J. H., and Welt, L. G.: Tropical Ulcers and Cutaneous Diphtheria, to be published. Norris, R. F.; Kern, R. A.; Schenck, H. P., and Silcox, L. E.: Diphtheria in the Tropics: A Report of Eighteen Cases on a United States Naval Hospital Ship, U. S. Nav. M. Bull. **42**:518, 1944.

Two series of patients will be considered. The first series was studied in the late winter and spring of 1943, when I was assigned to a general hospital in Melbourne, Australia.[3] It consisted of 13 members of the first Marine division, which was staging there at the conclusion of the campaign at Guadalcanal. These men had been in action for varying periods between early August and late December 1942. Some had been present at the initial landing, when food and medical supplies had been inadequate. Others had arrived late in the campaign, when supplies and food were relatively good. One patient was a member of a headquarters company, arriving late in the campaign, and had been on the island only forty days prior to evacuation.

TABLE 1.—*Data on Group of Patients Studied in Melbourne, Australia, in 1943*

Case No.	Date of Arrival on Guadalcanal	Development of Sore Throat	Interval in Days Between: Sore Throat and Onset of Neuritis	Interval in Days Between: Onset of Neuritis and Maximum Involvement	Classification as to Severity†	Cutaneous Ulcers	Total Spinal Fluid Protein, Mg. per 100 Cc.	Presence of Antibodies to Diphtheria Toxin
1	Aug. 7	Dec. 15	7	74	B	Yes	† Pandy	No
2	Aug. 7	Dec. 1*	30	36	B	Yes	38	Yes
3	Aug. 7	Nov. 30	3	23	A	Yes	52	Yes
4	Aug. 21	Nov. 15	15	65	B	No	42	Yes
5	Aug. 21	Nov. 5	25	73	B	Yes	92	No
6	Sept. 17	Oct. 15	10	114	C	Yes	66	No
7	Sept. 18	Nov. 15	45	24	B	No	100	....
8	Sept. 18	Dec. 1	60	25	C	Yes	197	Yes
9	Sept. 18	Nov. 23	14	29	C	Yes	82	No
10	Sept. 18	Oct. 15	10	136	A	No	30	Yes
11	Nov. 11	Nov. 20	30	61	C	No	101	No
12	Nov. 11	Des. 15	30	39	B	Yes	217	Yes
13	Nov. 12	Dec. 25	37	62	C	No	39	No

* The patient had had a moderately severe febrile illness but no sore throat.
† For the meaning of A, B and C see explanation in the text.

He had never been on a jungle patrol; his diet was adequate, and his living conditions were relatively good.

There was little, if any, close contact between the Marines and the natives, as most of the latter had taken to the jungle with the onset of the fighting. Contact with Japanese was limited to hand to hand combat and burial details. All had bathed in and drunk from the Lunga River and its tributaries. This is a sluggish tropical stream and almost certainly contaminated.

With 1 exception every member of this group gave a history of a severe sore throat from three to sixty days prior to development of any neurologic symptoms or signs. Eight of the 13 patients also gave a history of "sores" on the lower part of the legs and the feet during the campaign. The Marine without a history of sore throat had had an

3. These studies were carried out under the direction of Lieut. Col. Edward O. Harper, Medical Corps, Army of the United States

unexplained febrile illness thirty days prior to neurologic changes and was one of those with ulcers of the skin.

The data on these patients are summarized in table 1. Column 2 of the table shows the date of the patient's arrival on Guadalcanal. Five of the group arrived in August, 5 in September and 3 in November. Column 3 shows the date of onset of sore throat. There is no correlation between the time of arrival and the date of development of the sore throat except that no sore throats occurred prior to arrival on Guadalcanal. Column 4 gives the number of days elapsing between development of the sore throat and the onset of neurologic signs and symptoms. It is apparent that this is one of the most variable points in this series, and its variability is one of the most difficult to explain. Column 5 shows the number of days required for the neurologic disease to reach its maximum severity, and column 6 indicates the severity of the disease. Classification A included patients whose disease was mild, with merely evidence of involvement of peripheral nerves, mild sensory changes and loss of the deep reflexes. Classification B is one of medium severity. The patients, in this category, in addition to signs of involvement of peripheral nerves, also gave evidence of damage to cranial nerves and lesions of the spinal cord. They were likely to have a history of motor weakness, in spite of which they were never seriously incapacitated. In classification C in which all the patients showed evidence of severe neurologic disease, signs referable to the cranial nerves were conspicuous. These patients had pronounced weakness to complete paralysis of the extremities and marked ataxia. Two patients fell into classification A, 6 into classification B and 5 into classification C. It is apparent that the severity of the disorder bore little, if any, relation to the time required for the disease to reach its maximum. The time for the patients in classification A varied from twenty-three days to one hundred and thirty-six days; that for patients in classification B, from twenty-five to seventy-five days, and that for patients in classification C, from twenty-five to one hundred and fourteen days. Column 9 shows the results of studies on the serum of 12 of these 13 Marines for the presence of diphtheria antibodies. Six of them had demonstrable antibodies, and 6 had no antibodies. Column 8 shows the maximum protein levels of the spinal fluid for these patients. It is apparent that there is not much relation between the severity of the disease and the total protein of the spinal fluid. With 1 exception, only single determinations were made and it is possible that the correlation might have been better if the result of repeated taps over the entire course of the disease had been used.

Twelve of 13 patients were studied to determine whether their serum contained any antibodies against the diphtheria toxin. The Jensen

modification of the Römer test was employed.[4] Serums of these 12 patients were inactivated at 56 C. for fifteen minutes and then mixed in equal volumes with diluted diphtheria toxin. Two dilutions of toxin were used—one equal to twice the Schick test dose and the other to ten times the Schick test dose. The mixtures were then injected intradermally into the skin of 2 rabbits. Serums from 13 control patients, who were carefully questioned as to any previous history of sore throat or neurologic complaints, were treated in a similar fashion. The results of this procedure are shown in table 2. As is shown there, the serums of both the neurologic and the control group neutralized diphtheria toxin to approximately the same extent. The serum of only 1 patient was able to neutralize the higher dilution, but it failed to neutralize the lower dilution.

One patient (13, table 1) was treated for severe sore throat, which had developed approximately three weeks prior to his admission to the hospital. On his admission cultures showed hemolytic streptococci. No diphtheria bacilli were found on repeated cultures. He had typical

TABLE 2.—*Results of Titration of Serum Antitoxin*

	Total Number	Positive Schick Reaction × 2*	Positive Schick Reaction × 10*
Melbourne patients with neuritis.....	12	5	6
Melbourne controls	13	6	6

* Two dilutions of diphtheria toxin were used: one equal to twice the Schick test dose and the other to ten times the Schick test dose.

acute glomerulonephritis shortly after his admission. Thirty-seven days after the onset of his sore throat he manifested early neurologic changes, which gradually progressed to the point that he was unable to get out of bed. Titration of his serum on the skin of a rabbit failed to show any antibodies to diphtheria toxin.

It was felt, on the basis of this evidence, that in this particular group of patients the neurologic syndromes were nondiphtheritic in origin. A filtrable virus as the etiologic agent in a neurologic syndrome of this type has long been considered by some investigators.[5] An effort was made to isolate a possible virus agent by injecting pooled washings from the nose and throat and serums into the aminotic cavity of 12 day chick embryos, after the method of Burnet.[6] Spinal fluid was injected

4. Jensen, C.: Die intrakutane Kaninchenmethode zur Auswertung von Diphtherie-Toxin und Antitoxin, Acta path. et microbiol. Scandinav., 1933, supp. 14, p. 1. Römer, P. H.: Ueber den Nachweis sehr kleiner Mengen des Diphteriegiftes, Ztschr. f. Immunitätsforsch. u. exper. Therap. **3**:208, 1909.

5. Bradford, J. R.; Bashford, E. D., and Wilson, J. A.: Acute Infectious Polyneuritis, Quart. J. Med. **12**:88, 1919.

6. Burnet, F. M.: Influenza Virus Infections of Chick Embryo Lung, Brit. J. Exper. Path. **21**:147, 1940.

intracerebrally into Swiss mice. Stool emulsions, mixed with ether and left overnight at a temperature of 4 C., were injected intraperitoneally into monkeys. All these attempts to isolate a virus were complete failures—the embryos showed no changes, and all the test animals exhibited no ill effects.

It is unfortunate that it was not possible to follow these patients to complete recovery. For military reasons it was necessary to evacuate them to the United States as soon as they were able to travel. All

TABLE 3.—*Data on Group of Patients Studied at Moore General Hospital in 1945*

Type of Disease	Number of Patients	Average Interval in Days from: Initial Cutaneous Disease to Open Skin Disease	Average Interval in Days from: Open Skin Disease to Neuritis	Average Interval in Days from: Onset of Neuritis to Maximal Severity	Schick Tests, per Cent Positive Reactions	Classification as to Severity * A	B	C	Average Total Protein of Cerebrospinal Fluid, Mg. per 100 Cc.
Primary ulcers.....	17	..	91	45	35	2	6	9	83
Secondary ulcers.....	19	113	85	47	35	6	7	6	95
No ulcers.....	9	91	81	45	33	4	2	3	95
Cutaneous diphtheria	5	156	115	45	80	1	3	1	60

* For the meaning of classifications A, B and C see explanation in test.

TABLE 4.—*Data on Group of Ten Patients Who Had Severe Sore Throat During Course of Cutaneous Disease and Prior to Onset of Neurologic Symptoms*

Type of Disease	Number of Patients	Average Interval in Days Between: Sore Throat and Neuritis	Average Interval in Days Between: Open Cutaneous Disease and Neuritis	Average Interval in Days Between: Onset of Neuritis to Maximum Severity	Schick Tests, per Cent Positive Reactions	Classification as to Severity (See Text) A	B	C	Average Total Protein of Cerebrospinal Fluid, Mg. per 100 Cc.
Proved faucial diphtheria.....	2*	29	52	52	50	0	1	1	72
Probable faucial diphtheria; virulence tests not done	5	23	69	51	20	1	2	2	89
Severe sore throats but not diphtheria..	3	42	93	57	67	1	0	2	57

* One patient also had virulent organisms in the skin.

showed definite improvement before evacuation was requested. It was estimated that the total duration of the neurologic syndrome from onset to complete recovery in this group of patients averaged seven months, with a minimum of five months and a maximum of eight months. Most of this group had one or more malarial relapses during the course of their neurologic disease. Only 1 patient showed a questionable exacerbation of his neurologic signs. None of them showed any apparent neurologic symptoms as a result of antimalarial treatment—in this case

a quinine, quinacrine (atabrine) and pemaquine naphthoate (Plasmochin) routine.

The second group of patients, totaling 60, were at Moore General Hospital, Swannanoa, N. C., during the last three months of 1944 and the first nine months of 1945. They had all been evacuated from the Pacific theaters because of cutaneous disease. These data on these patients are summarized in tables 3 and 4. Table 3 deals with the 50 patients who gave no history of having had a sore throat. Of these, 17 patients had a history of "tropical ulcers" as the first manifestation of any disease of the skin. Nineteen stated that their tropical sores followed other types of cutaneous disease, including epidermophytosis, infectious eczematoid dermatitis and atypical lichen planus. Nine patients stated that they had never had any ulcers but did admit that their cutaneous lesions had on occasion been weeping or had been secondarily excoriated. There were 5 patients, or 10 per cent—4 with tropical ulcers and 1 with an eczematoid type of atypical lichen planus—cultures of whose skin were positive for C. diphtheriae.

It is evident from examining table 3 that the patients for whom positive cultures for diphtheria organisms were obtained had had cutaneous disease for a longer time than had the other three subgroups. The interval between the development of the open lesions and the onset of the neuritis was also somewhat greater on the average. Four of the 5 patients with proved diphtheritic neuritis had positive reactions to the Schick test at the time the cultures were positive, whereas for those patients from whom diphtheria organisms could not be obtained the reaction to the Schick test was positive in 35 per cent.

The patients were classified as to the severity of the neurologic disease by a scheme similar to that for the Melbourne group. The patients with primary ulcer had a higher percentage with disease of grade C severity than had any of the others. The last column in table 3 shows the average total protein of the spinal fluid for the four subgroups. The figure for the group with cutaneous diphtheria is considerably less than that for the others.

Table 4 summarizes the data on the 10 patients who in the course of their disease and prior to the onset of neuritis had severe sore throats. Of these, 2 had proved faucial diphtheria (1 of these patients also had virulent corynebacteria in the skin); 5 had probable diphtheria—on these no tests for virulence had been made—and 3 had sore throats from which no diphtheria bacilli could be isolated. Only the aforementioned patient had virulent organisms in the skin, and all the patients fell into the classification of "secondary ulcer" or of "no ulcer." Both patients with faucial diphtheria had received diphtheria antitoxin. Three months later 1 had a positive reaction to the Schick test and the other a negative reaction. Of the 5 patients with "probable diphtheria," none

of whom received antitoxin, only 1 gave a positive reaction to the Schick test. The classification into groups A, B and C and the results of determinations of the spinal fluid protein require no comment.

The results of Schick tests on this group are shown in table 5. When the 5 patients with proved cutaneous diphtheria and the 2 patients with proved faucial diphtheria are omitted, it is seen that the percentage of positive reactions is essentially the same as that for the control group. The control group here was obtained by analyzing the results of all Schick tests on male enlisted personnel, exclusive of this study group. If the 5 patients with "probable" faucial diphtheria had been excluded also, the percentage of positive reactions would have been slightly higher, inasmuch as 4 out of these 5 patients gave a negative reaction to the Schick test dose of toxin.

It is admitted, of course, that results of the Schick test, particularly in an adult group, are not entirely conclusive. Certainly, the presence of a positive reaction to the Schick test in a single patient would be of little or no significance, but it is also felt that in as large a group as

TABLE 5.—*Results of Schick Test*

	Total Number	Positive Reactions to Schick Test	
		Number	Per Cent
Moore: Patients with neuritis at General Hospital	54	19	35
Moore: General hospital controls	232	94	39

this one there should be some decrease in the percentage of positive Schick reactions if this neurologic syndrome were due to diphtheria.

Two interesting cases will be reported briefly. The first patient had the primary ulcers when he was on Leyte. Three weeks after their onset, while a patient in a general hospital, he suddenly experienced vertigo, deafness in the right ear and diplopia. These were followed by rapidly progressing weakness and loss of sensation in the extremities. He was evacuated to the United States and was admitted to one of the wards for diseases of the skin at Moore General Hospital. On admission his skin had cleared, but he showed the characteristic neurologic changes of the severe form (classification C) of this syndrome. His spinal fluid protein was over 100 mg. per hundred cubic centimeters, and his reaction to the Schick test was positive. Approximately one month later, and a total of two months after the onset of neurologic signs and symptoms, typical faucial diphtheria developed. This responded satisfactorily to antitoxin, and the Schick reaction became negative. It is reasonable to believe that had this man's neurologic symptoms been the result of the action of diphtheria toxin he should have shown some immunity—instead he was not immune and contracted diphtheria.

The second patient had been hospitalized for atypical lichen planus and had been evacuated to the United States. Approximately one month after arrival there he was ready for furlough. He awakened one morning and found that he had trouble in accommodating. In the next forty-eight hours severe weakness developed, and in a week he was bedridden, with complete quadriplegia. His spinal fluid protein was nearly 200 mg. per hundred cubic centimeters. This patient had not had a sore throat, nor had he had tropical ulcers. He did state that at one time the papules of lichen planus had been somewhat excoriated. This patient remained completely incapacitated for thirty-six days, before recovery set in.

SUMMARY

Two series of patients with a syndrome showing various degrees of involvement of the nervous system are presented. All but 1 of the first series had as a precursor to the neurologic changes a severe sore throat. This 1 patient complained of a febrile illness thirty days prior to any neurologic complaint. Eight of the 13 patients also had had "tropical ulcers" while on Guadalcanal. The sore throats as described were extremely severe and incapacitating for a matter of weeks. At the time that these patients were hospitalized in Melbourne, intensive investigation, with the cooperation of the medical officers of the United States Navy attached to the Marine Corps, failed to disclose anything suggesting that these patients had had diphtheria. There had been no reports of diphtheria on Guadalcanal so far as the medical officers stationed there were aware. There had been numerous patients with severe sore throat, and many of these had been studied for possible diphtheria, with completely negative results. If these patients had had diphtheria of this degree of severity, some deaths would have been expected, inasmuch as no antitoxin was administered. On the basis of the clinical study, the Schick test and the titration of diphtheria antitoxin in the serum, it was believed that the neurologic syndrome in this series of patients was not postdiphtheritic.

The second series, of 60 patients was studied at Moore General Hospital about two years later. In this series, 2 had proved cases of faucial diphtheria and 5 proved cases of cutaneous diphtheria. There were 5 others who probably had had faucial diphtheria but from whose cutaneous lesions Corynebacteria had never been isolated. The majority of the group showed no evidence of either faucial or cutaneous diphtheria but exhibited a neurologic syndrome which seemed to be the sequela of severe cutaneous disease.

The neurologic changes varied in severity, sometimes resulting in temporary complete paralysis of the limbs but ending in complete recovery in all cases which we were able to follow to completion. Whereas clinically this observation is not inconsistent with the neurologic

changes seen after diphtheria, it is felt that the evidence presented indicates that C. diphtheriae was not the causative agent of the neurologic syndrome in most of these patients.

CONCLUSIONS

1. Thirteen patients with a postinfectious neurologic syndrome were studied in the Fourth General Hospital in Australia in 1943. Attempts to isolate a filtrable virus were unsuccessful. There was no evidence to suggest that the condition of any of these patients was the result of diphtheritic infection.

2. Sixty patients with a similar disturbance were studied at Moore General Hospital in 1945. Of these, the neurologic syndrome followed proved cutaneous diphtheria in 5, proved faucial diphtheria in 2 and severe sore throat which was probably diphtheritic in 5 others. There was no evidence to suggest that diphtheritic infection had played any part in the disease of the remaining 48 patients.

2065 Adelbert Road, Cleveland 6.

INTRAVENOUS INJECTION OF SODIUM AMYTAL AS A TEST FOR LATENT ANXIETY

CAPTAIN SAMUEL SUSSELMAN
AND
CAPTAIN FRED FELDMAN
MEDICAL CORPS, ARMY OF THE UNITED STATES
AND
S. EUGENE BARRERA, M.D.
ALBANY, N. Y.

SODIUM amytal has been widely utilized in the investigation and treatment of mental disorders. Its effectiveness in probing and clarifying stuporous psychotic states and its value in alleviating major hysteria are examples of its usefulness, which find expression in the routine daily work of most psychiatrists. There is, however, an area in the field of psychiatry where sodium amytal has been little used, yet an area where its utilization may prove fruitful indeed. This encompasses the so-called anxiety or tension states, by far the largest category of the psychoneuroses.

The bulk of the conditions included under the clinical label of "psychoneurosis" cannot be adequately designated by such descriptively specific diagnoses as conversion hysteria, obsessive-compulsive states and hypochondriasis. Rather, they must be grouped together on the basis of the broad concept of tension engendered by frustration, thwarting and insecurity, and are consequently best and most simply described as the tension, or anxiety, states. The pattern of anxiety which the organism may display are diverse, but they can be demarcated and the symptoms of each pattern itemized. One such pattern, for example, may be tension expressing itself through the gastrointestinal tract. Another constellation of symptoms may be derived chiefly from the musculoskeletal system.

Among the musculoskeletal symptoms of anxiety in an individual patient one might find feelings of "drawing" in the temples, eyes and neck; severe occipital headaches; a feeling of unsteadiness while walking, and easy fatigability. This pattern of symptoms is not uncommon, is readily diagnosed as an anxiety state and is recognized as requiring psychotherapy.

Anxiety or tension symptoms, however, are not always readily recognized as such. When they appear in unusual constellations, or when isolated symptoms appear in patients not considered previously psycho-

From the Department of Neurology and Psychiatry, Albany Medical College.

neurotic, the origin of the complaints may be in doubt. Any individual anxiety symptom may therefore so closely resemble a symptom produced by a truly organic process that differentiation by the usual diagnostic tests may be impossible. So far as the patient's verbalization of his complaint is concerned, there is no significant difference between that of functional and that of organic origin. Nor, indeed, in the patient's awareness is there a difference. The headache resulting from tension in the muscles of the forehead and temples caused by anxiety seems as severe and as incapacitating as the headache produced by increased intracranial pressure. The nausea which accompanies the gastrointestinal pattern of anxiety is as real and sickening to the sufferer as the nausea of intestinal obstruction.

When it proves impossible to determine the existence of an organic basis for the patient's complaint, the physician may turn slowly to the concept of psychoneurotic causation. In most instances, however, the diagnosis of psychoneurosis is one evolved by the exclusion of every potential somatic cause, no matter how remote the likelihood of its presence. This process is often slow, costly and, in the end, unrewarding. We feel that it is possible to prove the "nonorganic" origin of many symptoms by a concrete diagnostic test. The test consists in the intravenous administration of small amounts of sodium amytal, injected fairly rapidly. Within one to five minutes, in most cases, the patient will note a definite abatement of his complaint if it is truly a tension symptom, and often in this astonishingly brief period he will report complete relief. We have used this test in a large number of cases presenting this confusing problem in diagnosis, with frequently gratifying results. This paper constitutes a report on our first series of such cases.

METHOD AND MATERIAL

Method.—The patient's symptoms should be sufficiently acute at the time of injection of the amytal to make possible to the awareness of the patient an appreciable degree of relief. The patient is therefore instructed, if he is hospitalized, to put in a call for the house physician when his complaint is most acute. If he is an ambulatory patient or an outpatient, he is instructed to await the period when his symptoms are most distressing and then come to the physician's office at once. We have also made use of the emergency room of the hospital for this purpose, keeping sodium amytal available there and undertaking to have a house physician respond to such calls as promptly as possible. If the patient is hospitalized, no special preparations are required; but on the completion of the test the floor nurse is advised that the patient has received a certain amount of the drug, and orders for observation are given. In most instances the patient's sensorium will in no way be impaired, but a few patients may manifest drowsiness, confusion, incoordination or, rarely, excitement. Ambulatory patients should be accompanied by a responsible adult, and adequate means of transportation home should be available in the occasional cases in which these side effects occur.

The patient is allowed to recline, and data on the exact nature and magnitude of his symptoms are elicited and recorded. Before the amytal is injected, the patient is encouraged to describe his difficulties as accurately as possible, and he is examined physically as completely as is necessary. He is told that he will be given an injection that may relieve his symptoms somewhat, but unduly strong suggestion is not attempted. The patient is warned, also, that he may note some dizziness immediately after the drug is injected but that this is harmless and will pass off.

The solution of sodium amytal should be freshly prepared, being dissolved in distilled water or in isotonic solution of sodium chloride just before injection.

Data in Cases of Anxiety Symptoms Treated with Intravenous Injections of Sodium Amytal

Presenting Symptom (by Systems)	Possible Diagnosis	Symptoms Entirely Relieved by Sodium Amytal	Symptoms Not Relieved or Only Partially Relieved by Sodium Amytal
Musculoskeletal			
Headache	Tension headache	22	5 (75-90% relief)
	Migraine (?)	1	3 (25% relief)
	Post-lumbar-puncture headache	4	3
Pain in shoulders and neck	Cervical neuralgia	3	0
Facial pain	Trigeminal neuralgia	3	0
	Sinusitis	1	0
Dizziness	Ménière's syndrome (?)	3	0
Ringing in ears	Ménière's syndrome (?)	1	0
Incoordination, unsteadiness of gait, (tremor), (blurring of vision)	Multiple sclerosis (?)	2	0
Pain radiating down leg	Sciatica	1	0
	Postoperative lame back	0	1 (made worse)
Gastrointestinal			
Nausea and/or vomiting	Ulcer or tumor (?)	23	1
Difficulty in swallowing	Esophageal ulcer (?)	2	0
Anorexia	Psychogenic	12	0
Epigastric distress (diarrhea)	Ulcer (?)	4	1 (50% relief)
Cardiovascular			
Anginal pain, (hot flashes), (palpitation), (tachycardia)	Angina pectoris (?)	2	0
Genitourinary			
Dysmenorrhea (frequency of urination)	?	5	2

The solution should be clear and colorless; occasionally we have encountered a brown or yellow solution, which may be attributed to impurities; such a mixture is discarded. We have been accustomed to use a solution containing 1 grain (0.065 Gm.) of sodium amytal in each cubic centimeter of solution, but other proportions are, of course, feasible. In most instances we have available, in the syringe, 4½ grains (0.29 Gm.) of the drug. One-half cubic centimeter (½ grain [0.032 Gm.]) of the solution is injected rapidly, and during the next thirty or forty seconds the patient is asked whether any improvement has been noted. There is usually no noticeable effect from this small amount, but occasionally the patient will report a definite degree of relief. Another 0.5 cc. is then injected, followed by questioning as to the extent of relief; and about one minute after the injection is started, the third 0.5 cc. is given.

Usually 1.5 cc. (1½ grains [0.097 Gm.]) is sufficient to produce significant relief; yet such an amount is so small that no drowsiness is evident, and no true analgesia can be said to have been produced. If the mitigation of the complaint is pronounced, no additional amytal is given. If the amelioration is only partial, however, it may be desirable to administer further portions of the drug, evaluating the persistence of symptoms as the injection continues and having in mind that as the total dose mounts many obscuring factors enter the picture.

Whether in the hospital or at home, the patient is observed carefully after the test to determine the interval of freedom from his symptoms.

Material.—More than 80 cases in which this test has been employed have been documented. The presenting symptoms are itemized in the accompanying table, where they have been classified according to the pattern of anxiety in which each is likely to find place. The arrangement of patterns of anxiety used here is a modification of that outlined by Cameron[1] and will be seen to embrace three categories of symptoms. The first column lists the presenting symptoms which patients exhibited to the physician, and the second column enumerates the organic illnesses considered as likely to account for the various symptom. It should be stressed that we have not encountered every possible symptom of tension in this series of difficult diagnostic problems. The entries enclosed in parentheses in column 1 of the table represent anxiety symptoms which have not as yet come to our attention in accredited cases and are considered of controversial origin. A glance through the list, however, makes it evident that any one of these symptoms may appear at times of debatable origin.

PAIN

HEADACHE

The largest group of cases falls in the category of symptoms referable to the musculoskeletal system, and the bulk of this group are cases in which pain was manifested in some form. The most numerous single class is that which includes different types of headache. The headaches were of many varieties, ranging from "full feelings" in any part of the head to headache described as severe, disabling and intensely painful. The headaches have been characterized as "spasms" and as "throbbing," "twinging," "piercing," "gnawing" and "torturing." Patients have described them as "bursting," as "feeling as if my brain were too big for my skull" or as "seeming as if some terrible pressure were trying to get out." The differential clinical diagnoses considered at one time or another included, among others, brain tumor, cervical neuralgia, migraine, hypertensive encephalopathy and syphilis of the central nervous system. Some headaches were of recent origin, while others had persisted for months or years, with little significant abatement.

The patient in whom the test is clearly successful will have no residuum of distress but will express, often spontaneously, great relief and complete freedom from pain and a feeling of well-being. This rapid lifting of discomfort is especially impressive to both patient and physician

1. Cameron, D. E.: Am. J. Psychiat. **101**:36-41 (July) 1944.

in cases of long-standing headache, which have remained unrelieved for months, or even years.

The awareness of reduction of tension has been expressed by the majority of patients, who usually describe the change as one of "relaxation." The symptoms of tension should be elicited by questioning before the injection of sodium amytal, as part of the case history of each patient. In most instances a definite constellation of anxiety or tension symptoms may be plotted, the most frequent pattern being that of musculoskeletal tension. The relief from these accompanying symptoms usually parallels the abatement of the headache, and the patient may state: "The drawing feelings in my neck and eyes are gone"; the tightness in my stomach has disappeared," or "the tightness in my arms and shoulders has gone."

Occasionally patients report a feeling of drowsiness concomitant with the sense of relaxation. The drowsiness is not marked, and no patient has fallen asleep with the injection of 1½ grains or less of sodium amytal. In a few instances patients who had been given between 2 and 3 grains (0.132 or 0.195 Gm.) disclosed, on subsequent visits, that they had napped on returning home. The question of the analgesic power of intravenous administration of sodium amytal is posed by this aspect of our results. It must be pointed out that the dose of 1½ grains of sodium amytal is sufficient to relieve the headache in most instances and results in no subsequent drowsiness. It is unlikely that so marginal a sedative dose will have analgesic potency, especially when symptoms are severe. Furthermore, relief from pain usually lasts longer than any possible pharmacologic effect of the drug. This will be considered in a subsequent section of the paper.

In each of the 22 cases of headache designated in the table we were able to effect prompt and unmistakable relief by means of the intravenous injection of less than 3 grains of sodium amytal. The usual dose was 1½ grains, but the dose required for complete relief in some instances was as low as ½ grain (0.032 Gm.). In a few cases 3 grains were necessary, yielding at times only partial amelioration. The case was not considered as meeting our requirements for inclusion in this series unless this partial relief was estimated as at least 75 per cent. In the series of cases in which significant relief from headache was obtained several may be presented as typical.

Tensional Headache.—The following cases are cited:

A man aged 26, a defense worker, for six months had had intense headaches, which started in the occiput and radiated over the vertex and down the back of the neck. He had received a series of injections of vitamin preparations and had secured no relief from acetylsalicylate acid and codeine. The pain was fairly constant but was more intense at the end of a day's work. With the injection of 1 grain of sodium amytal, the patient noted that the headache was gone but that there was some

stiffness of his neck. This was relieved with injection of ½ grain more, to give the patient complete relief of his symptoms. Psychiatric interviews revealed a number of problems which were judged to be contributory factors. He was given mild daily sedation and psychotherapy. When last seen the patient still had occasional headaches, but they were never so severe or so prolonged as formerly.

The duration of alleviation of headache is inconstant. In several instances the pain remained absent for weeks, whereas in others it recurred within a few hours.

The longest period of freedom was seen in the case of a woman aged 22, whose headache had persisted for more than a year. During that time she professed to have had no period of complete freedom from pain. After the injection of 2 grains of sodium amytal she acknowledged that the headache had vanished and stated that she was more relaxed and more content than she had been in over a year. She reported by telephone the next day that she was still free from pain, and she remained so for more than six weeks. During this time she felt so well that she was able to proceed with her plan to enter nurses' training, an undertaking she had postponed indefinitely because of the headache. The importance of associated psychotherapy in this case, as in all the others here discussed, is of course beyond dispute. The sodium amytal test is to be considered merely an adjuvant to diagnosis and therapy.

This patient's headache began to return in a mild form about six weeks after the first injection, despite several psychotherapeutic interviews. A second injection of amytal was given, complete relief again being obtained with 2 grains of the drug. The patient has now been free from symptoms for about three months and has also shown a decided improvement in the larger picture of her psychoneurosis.

In contrast to this case are those in which relief is gained for but a brief period, sometimes only a few hours. Although the duration is so limited, it is nevertheless evident that in many cases the appeasement persists longer than the known pharmacologic effects of the sodium amytal would lead one to expect.

One patient, for example, obtained almost complete relief by means of 1 grain of sodium amytal and was free for the remainder of the day and for the major portion of the next day, beginning to perceive the return of the headache in the evening. Subsequent injections were necessary, but during this period the underlying factors in her psychoneurosis were probed and intensive psychotherapy was instituted.

In several instances it was clear that the distress recurred as the sedative influence of the drug wore off. It should be stressed, however, that the most signal value of the test is the rapid, sometimes abrupt, deliverance from pain by a small dose of the drug. This strongly suggests the "tensional," or "nonorganic," origin of the symptom in many cases. The fact that relief does not persist indicates the broader problem of the whole psychoneurosis.

A patient securing only transient relief was a woman aged 28, who described her headache as "a terrible aching and pulling on the back of my head." She was able to carry on her work as a secretary, but without enjoyment, and had

surrendered her usual recreational and social activities. She visited the emergency room of the hospital several times, usually in the early evening, and with injection of from 1 to 2 grains of sodium amytal found solace, which she described as an "oasis" in the continual distress she felt. Her well-being usually persisted for the remainder of the evening, and she was able to fall asleep more readily than was customary. The following morning, however, saw the headache restored to its original severity. The patient refused to return regularly for psychotherapy and has as yet refused to enter the hospital for more intensive study; but the results of the amytal test, together with the history and the absence of positive physical signs, make the diagnosis of tensional headache probable.

A definite proportion of patients did not secure significant relief. One reason for failure of sodium amytal to give them relief was the probable presence of some organic cause. In certain patients, however, no organic factor was unearthed; yet the mitigation of the headache by means of sodium amytal was not sufficiently well defined to warrant their being included in the group with tensional headaches. Instead of replying within one to five minutes after the injection of the amytal that the headache had vanished, the patients sometimes qualified their statements by expressing uncertainty.

One patient explained that her headache had lessened somewhat but said, "There's still a funny feeling of pressure in the back of my head, sort of uncomfortable, and a little ache in the front."

A second patient who was included among those who failed to obtain relief described her headache, after sodium amytal had been injected, as "still present, I think, but it seems to be screened out a little by dizziness." The feeling of dizziness was sensed by many patients, but most of them found, nevertheless, that it did not obscure their awareness of definite relief of the headache. Thus, one patient stated, "My headache is gone completely, for the first time in months. I feel a bit dizzy, but no more than one cocktail might make me feel; the sense of relaxation is glorious."

Migraine.—The numerous problems of migraine and its psychosomatic implications are at issue here, but the evidence which has emerged in the present series is inadequate for us to assess the question basically.

Four patients with previous clinical diagnoses of migraine were tested, with inconclusive results. Three patients had partial alleviation of their headache, each patient estimating his relief as 25 per cent. One of these was a man aged 40 with a history of migraine for several years. Several therapeutic regimens had been followed, without complete relief from any. The injection of from 1 to 2 grains of amytal yielded partial relief, which lasted from one to seven or eight days; four such injections were given. The patient was given sodium amytal to take by mouth, in a dosage of 1 grain three times daily, with instructions to take 2 capsules of 1 grain each when a sudden, severe headache manifested itself. He has now been receiving this medication for a sufficient period to permit comparison of its value with that of ergotamine tartrate, the only drug previously used which had offered significant aid, and he reports that the amytal is definitely more salutary. The psychoneurotic background of this patient has been investigated at some length, and regular psychotherapy has reenforced the use of the drug.

Optimal relief is obtained by using ergotamine tartrate in combination with sodium amytal.

The pressure of "tensional" headache superimposed on the headache of migraine is recognized by many observers, notably Wolff.[2] Ergotamine tartrate followed by injections of sodium amytal might well afford more complete relief to sufferers of migraine than ergotamine alone.

The most startling relief was experienced by a hospital technician, aged 37, who had had periodic headache for the previous eighteen years. The diagnosis of migraine had been made, but she secured such inadequate relief from prescribed medication that she was forced to take to bed for one or two days during each episode. She was given 1 grain of sodium amytal by intravenous injection at the beginning of a typical attack of headache, with almost complete and immediate relief. A second headache, four weeks later, was relieved at home by taking seconal sodium (1½ grains [0.097 Gm.]) orally. For the past three months the patient has had no recurrence of symptoms.

Post-Lumbar-Puncture Headache.—Seven patients with post-lumbar-puncture headache were tested with sodium amytal by the method noted. All injections were administered at least eight hours after the lumbar puncture, and usually on the following day. Four patients noted significant and rapid relief.

One of these was a kitchen helper aged 38 who had first had seizures about two years prior to admission to the hospital. After lumbar puncture he had severe headache and nausea, which were relieved by lying down. These symptoms persisted for two days despite medication with acetylsalicylic acid and codeine. On the third day he was given sodium amytal, 1½ grains, with complete relief of pain. This relief persisted all that day, and the patient was discharged the following day, still free of headache. In another patient, however, freedom from pain lasted one hour, and the headache returned with its former severity.

Head Pain Other Than Headache.—The face, neck and shoulders are common sites for the appearance of the "drawing pains" which form a part of the musculoskeletal pattern of anxiety. These regions, too, are areas where differential diagnosis as to the origin of the pain may constitute a formidable problem. Included in the present series are several cases of this type, in each of which the usual clinical and laboratory tests were uninformative but the headache was demonstrated to be of tensional origin by the amytal test.

Pain in the posterior part of the neck and shoulders, resembling cervical neuralgia, was relieved in 3 cases—all those which were investigated by this means. In each instance there was pain sufficiently severe to bring the patient to his physician, and in 2 cases the pain was sufficiently agonizing and persistent to make hospitalization advisable when the local physician was unable to ascertain the cause. Careful histories revealed the general psychoneurotic background of the patient's behavior,

2. Wolff, H. G.: J. Omaha Mid-West Clin. Soc. **5**:33-39, 1944.

but the pain in the shoulder could not be considered incontrovertibly an anxiety symptom until the amytal test was applied.

Facial pain resembling trigeminal neuralgia was encountered in 4 cases in this series, and pain simulating that frequently present in sinusitis was seen in 1 case. The diagnostic problems were similar to those noted previously, in that trigeminal neuralgia was judged to exist after other possibilities had been exhausted by roentgenographic and other examinations. The distribution of pain in each case was not closely characteristic of trigeminal neuralgia, nor was the type of attack representative; but no other diagnosis seemed feasible to the referring physicians. Sodium amytal evoked significant relief in each case.

The most perplexing case was that of a nurse aged 42, whose trouble had been diagnosed as tic douloureux by her referring physician. She had been thoroughly studied for evidence of sinusitis, a complaint she had voiced intermittently for several years, without anything positive coming to light. She described her distress as being fairly constant on a low grade level, with frequent episodes of harsher pain, sometimes so unrelenting as to cause crying. The pain involved the left side of her face, beginning near the ear and spreading to the nose, temple and chin, and being accompanied with headache. Later in her stay in the hospital she complained that there was some involvement of the opposite side of the face, though to a less, and much more bearable, degree. This case was at first studied as purely neurologic, and the lassitude and dejection she displayed were considered to stem from her oppressive pain. It quickly became apparent, however, that emotional factors were of paramount import, and interviews disclosed a multitude of conflicts and anxieties. It was still not possible to establish the tensional origin of the pain, although our suspicions were alined in this direction. The injection of 2 to 3 grains of sodium amytal brought about startling relief, which persisted for several hours. The patient's subsequent course included intensive psychotherapy, bolstered by several injections of amytal at critical moments of distress. It became evident that her tensional symptoms were colored by an undercurrent of depression, which did not respond to psychotherapy. The element of depression was soon judged so grave, although somewhat hidden, that electric shock therapy was decided on. She improved rapidly during a course of six shocks, and on discharge was almost completely well—not depressed, and free from her facial pain, although still voicing many of her basic anxieties.

PAIN IN PARTS OF THE BODY OTHER THAN THE HEAD

"Sciatica."—Another case of pain difficult to diagnose was one of sciatica.

A woman aged 30 had been under treatment for sciatica. The attacks usually began mildly with shooting pains down the posterior aspect of the left leg. She was placed on a regimen of rest and physical therapy but did not improve rapidly, so her physician brought her into the hospital, where roentgenologic and neurologic examination and studies of the spinal fluid showed nothing abnormal. One evening she complained that the pain was increasing, and as the night went on she insisted that the anguish was becoming unbearable. Codeine and seconal sodium brought some relief, but a second dose of seconal was necessary to produce sleep. She complained of still greater agony the next day; in addition, she was agitated,

apprehensive and tremulous. Sodium amytal was injected slowly. When only ½ grain had been introduced, she began to relax, said she was less tense and reported definite improvement in the pain in her leg. With only 1 grain of amytal injected into her blood stream, she began to express wonderment that her wretchedness had left her so completely and reported that her leg was free from pain. She demonstrated this fact by moving the limb readily, although she had for the previous several days held it almost immobile. She was discharged from the hospital shortly afterward; later she had two episodes of pain, which were again relieved with sodium amytal. With psychotherapy she remained symptomless for almost a year.

Postoperative Lame Back.—In only 1 instance was pain made worse with sodium amytal.

A man aged 33 had been operated on for a ruptured intervertebral disk about eight months prior to the present admission. At that time a fusion of the spinal vertebrae had been done. After recovery the patient was subject to recurrent pain in the back, which radiated down both legs and was relieved by his remaining in bed for a time. However, on his resuming work the pain would recur with its old intensity. He was seen by several physicians, one of whom told him that he had a "chronic lame back" and another stated, "It's just your imagination." To alleviate his pain, the patient began to drink more heavily than before and was first seen by us in the psychiatric ward during an acute alcoholic episode. When he recovered from the effects of the alcoholism, he was discharged and made a good social adjustment, with the help of Alcoholics Anonymous, Inc., which helped him secure a job as a dental mechanic. After working for several weeks at tasks requiring his sitting for eight hours a day, the patient began to complain of severe pain in the back. He was given an injection of 2 grains of sodium amytal, but this only increased the pain. He was thereupon taken into the hospital, where an intraspinal injection of iodized poppyseed oil revealed still another ruptured intervertebral disk. This was removed, and the patient has had no recurrence of the symptom since the operation, three months ago.

Dysmenorrhea.—One of the most perplexing and annoying symptoms is that of dysmenorrhea. Often women are relieved by surgical procedures, such as dilation and curettage, placement of stem pessaries and suspension of the uterus. Hysterectomy is at times resorted to in cases of persistent and incapacitating dysmenorrhea. We have treated 7 patients with dysmenorrhea and have failed to afford relief in only 2 of these patients. Each patient was given 1½ grains of sodium amytal intravenously. Relief from pain persisted throughout the day (usually the first day of menstruation) except for minor, negligible cramps.

"Anginal" Type of Pain.—We have diagnosed as tensional the pain of 2 patients with syndromes of angina pectoris by relieving symptoms through intravenous injections of sodium amytal.

One of these patients, a woman aged 52, whose first husband had died of coronary occlusion, experienced repeated pain in the precordium, which radiated down the left arm. Electrocardiograms on several occasions were normal.

Glyceryl trinitrate served to increase the symptoms, which responded completely to intravenous injections of sodium amytal in small doses.

SYMPTOMS OTHER THAN PAIN

Gastrointestinal System.—Many tensional symptoms are associated with the gastrointestinal tract. Included among these are nausea and vomiting, difficulty in swallowing, anorexia and epigastric distress. In 43 cases the symptoms were diagnosed as being cardinally functional by means of sodium amytal, which, injected intravenously in small doses, granted almost complete relief in all but 1 case.

Anorexia, even in depressed patients, is continually relieved by the administration of a relaxing dose of sodium amytal (usually 1½ grains) just before each meal. In the 12 instances of anorexia cited in the table, the patient was enabled by this method to eat entire meals without difficulty. Furthermore, none of these patients complained of a sense of fulness or nausea afterward.

One patient, a woman aged 53, had been undergoing medical treatment for difficulty in swallowing. Fluoroscopic examination showed a dilated esophagus, and the diagnosis of cardiospasm was made. Esophagoscopic examination failed to reveal any organic lesion which might be responsible for her condition. Sodium amytal, given intravenously in doses of 1 to 1½ grains during meals, when the patient complained of obstruction and regurgitation, enabled her to swallow without difficulty. The same sedation before meals gave her complete relief and did away entirely with the feeling that food was lodging in the esophagus. Her weight, which had dropped from 130 to 100 pounds (59 to 45.4 Kg.), began to rise. She was discharged with instructions to take seconal sodium before each meal. This procedure, together with psychotherapy, has allowed her to continue for the past two months without recurrence of her difficulty.

Twenty-three patients with nausea and/or vomiting obtained complete relief from their distressing symptoms, although for some of them a tentative diagnosis of peptic ulcer had been made.

Another patient with many symptoms of tension had been treated medically for diarrhea over a period of four years. She was seen by us because of "nervousness," incoordination and feelings of tension. These symptoms had been precipitated by the nature of her work, which required that she complete an assignment by a certain date. Although the patient realized that she should slow her pace, financial considerations made this impossible. After pointing out the hazards of continuing her work, we offered to support her by injections of sodium amytal at times when she was particularly distressed, with the understanding that when her work was finished she would enter the hospital for study and psychotherapy. Injections were given about every two days, with some relief of symptoms; interestingly, the patient reported that for the first time in years she had a formed stool, that she no longer suffered from diarrhea and that she had gained 7 pounds (3.2 Kg.) in three weeks.

The 1 patient with gastrointestinal complaints who failed to secure relief was a woman with severe nausea and vomiting which failed to yield to the relaxation produced by the drug and who finally required gastroenterostomy to obtain release from the symptoms. Adhesions were found around the duodenum, but no reason for a mechanical block of the pyloric outlet was discovered. The patient was discharged after an uneventful postoperative course and returned to her home.

Reports from one of her physicians indicated that the nausea and vomiting recurred, but further contact with this patient could not be made and we are uncertain as to her outcome.

Musculoskeletal System.—Many of the symptoms listed in the table under the musculoskeletal system have been discussed in connection with pain. The symptoms not discussed include those occurring in several cases tentatively diagnosed as Ménière's syndrome because of dizzy spells and ringing in the ears and a disturbance in 2 cases diagnosed as multiple sclerosis because of incoordination and equivocal signs. The patients were completely freed of their symptoms by injections of sodium amytal.

COMMENT

The broad concept of this paper is the contention that symptoms resulting from tension or anxiety will frequently disappear with mild sedation. In order that the effect of the sedative be fully appreciated, it should be given intravenously, to reduce the time between its administration and its effect. Furthermore, to eliminate whatever analgesic effects may be attributed to the drug, just enough sedative should be given to produce relaxation. This has been accomplished with sodium amytal in average doses of 1½ grains. The injections are made when the symptoms are at their height. Even when pain is the symptom, the mechanism of relief may be attributed to the tension-relaxing phenomenon, since the analgesic property of such small doses of sodium amytal is slight. None of our patients were put to sleep with these injections. Moreover, the relief afforded by the drug in most cases far outlasted its pharmacologic effect.

It should be stressed that this test should not supplant any of the customary psychiatric diagnostic procedures but is best utilized as an adjuvant to these procedures. It cannot replace the careful, comprehensive study of each psychoneurotic patient, involving the psychiatric interview, projective procedures for unearthing conflicts and other technics. It has served, however, in more than 80 cases encountered in a period of nine months to curtail the period of hospitalization of many patients.

Many patients are recognized as displaying definite neurotic patterns but as having also somatic complaints which are not necessarily part of this pattern and are therefore difficult to evaluate. For example, severe headache may be a cardinal complaint in a patient with chronic anxiety but may not have an organic basis. A careful history may reveal the place of the headache in the psychoneurosis, or psychotherapy may eventually relieve the headache, together with the other symptoms. It is felt that by means of this test, however, the proper assessment of the headache can be made more quickly, thereby saving both time and the expense of repeated searching for an organic foundation.

Although the test should not replace standard diagnostic procedures for organic illness, it has proved valuable in its role of focusing attention on functional elements in cases in which physicians have kept patients hospitalized for weeks in unavailing repetition of tests for organic disease.

The amytal test should be considered primarily a diagnostic measure. The problem of diagnosis in psychiatry is somewhat different from that in other specialties, for therapy goes hand in hand with diagnosis. From the moment the psychiatric interview begins, whether involving face to face discussion, projective procedures or use of the needle and syringe, treatment of the patient is instituted. The very willingness of the interviewer to probe into psychiatric problems should hold his awareness that he assumes therapeutic responsibility also. It is apparent therefore that no psychiatric test can be deemed solely a test. There must be continuous integration with therapy, in whatever degree required. The utilization of the amytal test must be governed by this tenet. Although primarily a diagnostic method, the relief of pain, the explanation of what is being attempted, the assumption of the patient-physician relationship—all of these constitute therapy and are inseparable from the simple diagnostic test. In the case histories previously cited, therefore, the diagnostic and therapeutic elements are necessarily mingled. Emphasis in this paper, however, is placed on the diagnostic value of the test.

The usefulness of this test is of course limited by the inherently complex nature of psychiatric problems. Its applicability, however, proved wider than we at first appreciated. Over the period of about six months during which our cases were collected, almost every service of a 600 bed general hospital called on the psychiatric department for consultation when this test proved fruitful. Considerable enthusiasm for the test was aroused in the departments of surgery, internal medicine, orthopedics and gynecology, where in puzzling cases the drug granted relief from symptoms after the usual procedures proved unavailing and the way was thus paved for future management. In many cases this initial relief of pain convinced patients and their families who were resistive to psychiatric consultation that further psychiatric therapy might be helpful. This is an important consideration in the care of private patients who refuse, because of their own or their families' unwillingness, to permit the sometimes slow tempo of psychotherapy to prove its value.

No one group of problems considered here is a statistically large sample, and the conclusions drawn for any one symptom complex must be considered tentative—indeed, they are not conclusions so much as reports on clinically interesting and therapy-resistant material. But although no one syndrome has been studied in large numbers, the fundamental pattern of the relief of pain, vomiting and other symptoms

by a tension-reducing measure has emerged in the entire series here reported.

This test shows that certain symptoms are based on what, for want of a more specific term, we call a tensional foundation. It also strengthens the belief that in many cases of organic disease there is a superimposed element in the system which is due to tension alone—probably the portion which makes the symptom so intense.

There has been a recent tendency to combine analgesic drugs with a sedative for optimal results. This is an empiric way of treating a symptom whose basis is not truly known. By use of the amytal test it can be determined whether the symptom is, in general, organic or functional and the proper drug utilized. In some instances the combination of an analgesic and a sedative drug would be more effective. Another advantage afforded by this test is that it can be used to prove the existence of tension to the patient and thus to lay the foundation for the future psychotherapy.

It must be stressed again that this test is primarily a diagnostic measure, that it should be considered only a small portion of the psychotherapeutic regimen and that each patient must be studied carefully as a problem in human behavior.

CONCLUSIONS

1. Anxiety or tension states may give rise to symptoms referable to many systems of the body, even in patients not considered psychoneurotic.

2. Symptoms due to organic disease may be exacerbated because of tension.

3. Sodium amytal in average doses of 1½ grains (0.097 Gm.) given intravenously will frequently relieve a symptom which is entirely due to tension within one to five minutes.

4. The same amount of sodium amytal will relieve that portion of the symptom due to tension in instances in which tensional pain is superimposed on pain of organic cause.

5. Sodium amytal in small doses can be used as a diagnostic test to separate symptoms of organic disease from tension symptoms.

6. The test should be used only to supplement thorough physical and psychiatric investigation.

Abstracts from Current Literature

EDITED BY DR. BERNARD J. ALPERS

Physiology and Biochemistry

ELECTRO-ENCEPHALOGRAPHY IN CASES OF SUB-CORTICAL TUMOUR. W. G. WALTER and V. J. DOVEY, J. Neurol., Neurosurg. & Psychiat. **7**:57 (July-Oct.) 1944.

By means of automatic analysis with an apparatus which traces a frequency histogram over the primary record, Walter and Dovey were able to make an exact analysis of the electroencephalograms in 31 cases of subcortical tumor. In all cases significant activity in the 4 to 7 cycles per second band was noted. Of these, good correlation between the superficial location of this rhythm and the deeper effects of the new growth was shown in 21 cases. These cases were divided into three categories, as follows: (1) Cases of superficial tumors spreading into subcortical structures. The site of the tumor exhibited activity of 1 to 3 cycles per second, or delta waves, while the adjacent areas and temporoparietal regions showed 6 cycles per second activity, or theta waves. (2) Cases of deep tumors spreading outward. The main feature was 6 cycles per second activity in the cortex above the tumor and in the temporoparietal regions. (3) Cases of deep tumors not affecting the cortex. The 6 cycles per second rhythm was the only significant abnormality, and this was usually related to the parietotemporal region. In cases in which the new growth was more widespread, the 6 per second rhythm was seen whenever basal structures were affected. Thus, an electrical activity of about 6 cycles per second is associated with involvement of subcortical structures, and this theta rhythm is located in the parietal and temporal regions.

MALAMUD, San Francisco.

THE EFFECT OF PERCUSSION OF NERVE. D. DENNY-BROWN and C. BRENNER, J. Neurol., Neurosurg. & Psychiat. **7**:76 (July-Oct.) 1944.

Denny-Brown and Brenner investigated the effects of lesser degrees of injury to peripheral nerves in order to determine the nature of the structural change underlying the transient disturbance of function with such injuries. They found that a single percussion of a nerve trunk resulted primarily in damage to the myelin sheath and probable longitudinal rupture of the sheath of Schwann, with escape of damaged myelin into the endoneural spaces but without interruption of the axis-cylinder, even with severe blows. At the site of injury a localizing swelling, or pseudoneuroma, developed as a result of edema associated with the rapid appearance of large numbers of histiocytes. This reaction was related to the breakdown of myelin and occurred if regeneration was prevented by proximal ligature. It was prevented if the blood supply was interrupted. With such a moderately severe lesion, since axis-cylinders remained largely intact, there was retention of sensation with transient complete block of impulses in motor fibers. This dissociation in function closely resembled that caused by ischemia induced with compression. The degree of edema and demyelination was lessened by concomitant rupture of the perineurium and decompression of the edema, indicating that ischemia accompanied the edema but was not an essential feature of the mechanism of the lesion. The phagocytic reaction was derived from histiocytes, the Schwann cells playing no part in it. A partial lesion produced transient paralysis, lasting three to four days, without loss of gross sensation. Here a

pseudoneuroma was also present, the majority of the axis-cylinders being deprived of myelin in passing through the neuroma but recovering it below. If the axis-cylinder was transversely interrupted by the percussion, degeneration occurred in the distal portion of the nerve fiber, and regeneration was extremely rapid and complete. Regeneration of axis-cylinders in intact Schwann tubes took place by the initial production of a large number of fibrils by the parent axis-cylinder, early maturation of one of these and resorption of the remainder. Delay in regeneration resulted when the perineurium was ruptured, causing herniation of nerve fibers and endoneurium with formation of a true neuroma. Percussion of a nerve trunk in the process of wallerian degeneration led to liberation of intratubal phagocytes by the mechanism of traumatic splitting of the tube of Schwann cells.

MALAMUD, San Francisco.

THE ELECTRO-ENCEPHALOGRAPHIC LOCALIZATION OF INTRACRANIAL NEOPLASMS. W. A. COBB, J. Neurol., Neurosurg. & Psychiat. **7**:96 (July-Oct.) 1944.

In an analysis of the electroencephalograms of 125 patients with intracranial space-occupying lesions, Cobb found that rapidly growing lesions near the free convexity of the cerebrum lend themselves most readily to localization. Thus, about one-half the cerebral tumors were correctly localized, as compared with only 3 of 21 subtentorial tumors and none of the midline or basal tumors. Localization was difficult in the case of parasagittal tumors, especially meningiomas. There was a greater tendency to slowing of the alpha rhythm in cases of tumor than is observed in cases of traumatic injury or of epilepsy. At times a noticeable asymmetry of the alpha rhythm was a useful aid in lateralization. The effect of increased intracranial pressure on the electroencephalogram was not characteristic, the abnormal waves being generalized and usually possessing a frequency of about 2 to 4 per second, irregular rhythm and lower amplitude than that of the alpha rhythm. This electroencephalographic pattern could not be distinguished from that of cortical atrophy, vascular disease or other diffuse condition. There was no direct relation between these changes and the height of intracranial pressure or the degree of papilledema, but there was some correlation with the state of consciousness. The local effects were not always distinguishable from the generalized effects of high pressure, but as a rule high amplitudes and very slow frequencies were uncommon with the latter. The usual record in a case of tumor was a mixture of slow frequencies.

The "ideal" means of localization is the finding of phase reversal of the slow waves, but not infrequently one must depend rather on their maximum intensity. A 4 to 7 per second frequency band, or theta rhythm, was found to be associated with lesions in the region of the third ventricle. In the opinion of the author, minimal general change may prove to be just as diagnostic in cases of tumor as the presence of a gross dysrhythmia.

MALAMUD, San Francisco.

THE ELECTROENCEPHALOGRAM IN TRAUMATIC EPILEPSY. D. WILLIAMS, J. Neurol., Neurosurg. & Psychiat. **7**:103 (July-Oct.) 1944.

Williams investigated the relationship of abnormalities in the electroencephalogram of patients with head injuries to subsequent onset of traumatic epilepsy by comparing the tracings of the following groups: (1) 241 normal healthy controls, (2) 234 patients with head injury but without epilepsy, (3) 210 patients with traumatic epilepsy, (4) 275 patients with idiopathic epilepsy and (5) 42 patients who were examined with the electroencephalograph before and after the onset of traumatic epilepsy.

The results showed that larval epileptic outbursts were invariably associated with overt fits, being present in 9 per cent of patients with traumatic epilepsy, in 27 per cent of patients with idiopathic epilepsy and in none of the subjects who

had not experienced epileptic fits, including those with head injury. Other paroxysmal outbursts, on the other hand, were nearly as common in patients with head injury who did not have fits as in those who did. Thus, the presence of other paroxysmal outbursts in cases of post-traumatic states does not necessarily indicate the development of traumatic epilepsy. Nonspecific abnormalities were not affected by the presence of epilepsy and represented results of injury or pre-traumatic abnormality. The incidence of paroxysmal epileptic outbursts was higher in the group of patients with penetrating wounds than in those with closed injuries of the head, while nonspecific abnormalities were equally common in the two groups. A comparison of the records made before and after the onset of fits showed that the characteristic episodic changes often appeared in the electro-encephalogram before the onset of traumatic epilepsy. Foci of abnormal discharge were found in a larger proportion of patients with traumatic epilepsy than in patients with idiopathic epilepsy. In the opinion of the author, a distinction is to be made between the immediate, or primary, effects of trauma on the electro-encephalogram which are reversible and transient, and the remote, or secondary, effects, which are irreversible and persistent and are usually associated with epilepsy. While the electrical disturbances associated with traumatic epilepsy and those occurring with idiopathic epilepsy differ in their frequency and site of origin, they are fundamentally similar. This conclusion may be compared with similar ones reached on histologic grounds.

MALAMUD, San Francisco.

THE SCOPE AND LIMITATIONS OF VISUAL AND AUTOMATIC ANALYSIS OF THE ELECTROENCEPHALOGRAM. G. D. DAWSON and W. G. WALTER, J. Neurol., Neurosurg. & Psychiat. **7**:119 (July-Oct.) 1944.

Visual inspection and measurement are often inadequate to analyze the more complex types of change present in an electroencephalographic record. Dawson and Walter use an electromechanical method of automatic analysis, by means of which mixed rhythms are synthesized and the effects on the form of such rhythms of variations in the size and frequency of their components are demonstrated. Visual examination does not separate from masking rhythms those component rhythms in a record which are masked. Moreover, only rhythms which are larger than others can be measured by the visual method, but those rhythms which are either comparable in size with or smaller than others are not measured by this method. To determine these, automatic analysis must be used. When the latter is not available, the use of closely spaced bipolar electrodes is of value, since it may demonstrate the presence of masked rhythms, although it does not measure their size. On the other hand, the limitation of automatic analysis is the inability of the method to record transient outbursts of brief duration and to express the phase relations of the components of a compound rhythm. The importance of the latter is seen in the simple cases of waves formed from a fundamental and one or two harmonics, as well as in the complex wave and spike discharges. Further investigations of these problems by full automatic analysis are indicated.

MALAMUD, San Francisco.

Neuropathology

HEPATOLENTICULAR DEGENERATION (WILSON'S DISEASE): REPORT OF ONE CASE WITH SEVERE PORTAL CIRRHOSIS AND SPLENOMEGALY. HARRY FREEDBERG, Ann. Int. Med. **22**:418 (March) 1945.

Freedberg reports the case of a 26 year old Italian woman with hepatolenticular degeneration who was closely observed over a period of six years. When she was first seen, she complained of extreme nervousness, periods of amenorrhea and coarse tremors of both hands. She adjusted fairly well, with little progression of symptoms, until five years after she was first studied, when she complained

of loss of weight of about 25 pounds (12 Kg.), bleeding from the gums, increase in nervousness and the development of an abdominal mass.

Physical examination revealed a protuberant abdomen with physical signs of ascites and evidence of splenomegaly. The liver could not be palpated.

The significant observations on neurologic examination were as follows: a constant grin, which remained relatively fixed; slow and monotonous speech, and some difficulty in swallowing. There were gross tremors of the head, protruded tongue and trunk and tremors of the extended hands; these tremors were increased with involuntary movement, especially on the left side. Slight tremor of the legs was apparent. There was a Warner hand on the left side. The deep reflexes of the upper extremities were of the basal ganglia type; that is, with each reflex response there was imperfect relaxation. This was also true to a less extent in the lower extremities. Examination with the slit lamp showed no evidence of a Kayser-Fleischer ring.

Rontgenographic examination showed extensive abnormalities involving the whole length of the esophagus. These consisted of tortuous defects of the mucous membrane. The changes were characteristic of extensive varicosities of the esophagus. The urine was normal. Studies of the blood revealed nothing of particular significance, except for anemia and negative Hinton and Wassermann reactions of the blood on two occasions and a positive Kahn reaction on two occasions.

Tests of hepatic function gave the following results: The prothrombin time was thirty-five seconds. The total cholesterol measured 107 mg.; the free cholesterol, 40 mg., and cholesterol esters 67 mg., per hundred cubic centimeters. The bromsulfalein excretion test showed a retention of 50 per cent of the dye at the end of an hour. The icteric index was 12. The total bilirubin of the blood measured 1.4 mg., and the blood phosphatase 6.0 Bodansky units, per hundred cubic centimeters. The blood serum proteins measured 7.10 Gm., with 2.95 Gm. albumin and 4.15 Gm. globulin, per hundred cubic centimeters. The Takata-Ara test was positive in four tubes.

For several months prior to death the patient had hemorrhages from the mouth, associated with vomiting and tarry stools.

Changes of significance observed at necropsy, other than the presence of esophageal varices, splenomegaly and ascites, were confined to the liver and brain. The liver was small, firm and uniformly nodular. Microscopic examination revealed definite thinning around many of the central veins, and a lobular pattern was present. In some sections there were broad areas of scarring and in others the lobules showed only slight vacuolation of some of the liver cells. A few portal areas showed slight increase of stromal connective tissue. The dura was not remarkable. The brain was described as being distinctly "porky" and edematous. On the left, in the region of the caudate nucleus, there were a grayish white area of apparent gliosis and some distortion of the relations of the nuclei to each other. The right side appeared to be entirely normal. The brain weighed 960 Gm.

Microscopic study of sections of the brain revealed no abnormalities except in the lenticular region, where there were occasional areas of loss of normal outline, with fraying of some of the structures and occasional foci of gliosis. Only an extremely rare large Alzheimer cell was seen. The appearance of the cortical cells showed no apparent lesion involving the third nuclear layer.

Freedberg reports this case because the changes affecting the liver far outstrip those observed in the lenticular nuclei, and death was directly related to cirrhosis of the liver. Wilson stated that the latter condition rarely, if ever, gives rise to symptoms during the life of the patient, and in the case described in the literature death was attributed to the cerebral involvement.

Tests of hepatic function which were performed before the patient's death indicated severe hepatic dysfunction. The positive Kahn reaction is explained by the hyperglobulinemia.

Freedberg believes that Wilson's theory, "that the liver is first affected and that the lenticular lesions follow as a result of some unspecified toxin which either originates from, or is not neutralized by, the damaged liver," is the most plausible explanation for the course of this patient's illness.

GUTTMAN, Philadelphia.

PATHOLOGY OF THE LIVER IN EXTRAPYRAMIDAL DISEASE. G. HEILBRUNN, O. FELSENFELD and P. SZANTO, J. Nerv. & Ment. Dis. **102**:19 (July) 1945.

The authors made postmortem examinations of the liver in 3 cases of post-encephalitic parkinsonism, 1 case of paralysis agitans and 1 case of Huntington's chorea and found mild and nonspecific structural changes, consisting of moderate periportal round cell infiltration, mild passive congestion and moderate fat infiltration at the periphery of the acini. The colloidal gold test of the blood serum, determination of the prothrombin time, the Weltmann coagulation test and the Lange-Heuer flocculation test were performed on 58 patients suffering from various extrapyramidal disorders, positive reactions being obtained in 85 per cent of the cases. The highest percentage of positive reactions (93 per cent) was found in 15 cases of Huntington's chorea. The authors believe that these results justify the conclusion that the liver manifests dysfunction in a high percentage of cases of extrapyramidal disease, but they feel that no conclusion as to its primary, secondary or correlated character is warranted.

CHODOFF, Langley Field, Va.

ANATOMICAL DEFECTS AND PATHOLOGICAL CHANGES IN CONGENITAL CEREBRAL ANEURYSMS. FRANCIS M. FORSTER and BERNARD J. ALPERS, J. Neuropath. & Exper. Neurol. **4**:146 (April) 1945.

Forster and Alpers report their histopathologic observations on 8 patients with cerebral aneurysms. The arteries of origin were embedded in paraffin, sectioned serially and prepared with hematoxylin and eosin, Van Gieson's stain for elastic tissue and Masson's trichrome stain. The condition of the parent vessel in the entire series of sections, the constituent coats of the aneurysmal sac and the changes in the wall of the vessel at the origin of the aneurysm were studied.

The cases studied revealed a variety of changes in the elastic membrane, ranging from a complete membrane, through splitting and fragmentation to the complete absence of the membrane, with a sharp defect at the site of origin of the aneurysm. These observations indicate that there is a tendency for the elastic membrane within the aneurysmal wall to disintegrate and that this occurs without other evidence of degenerative change, either in the elastic membrane of the parent vessel or in other structures of the aneurysmal wall. The tendency toward destruction of the elastic membrane may proceed not only until the entire elastica of the aneurysmal sac is destroyed but until even the edge of the defect is sharpened.

The present series of observations conforms with the prevailing opinion that the defect in the media is congenital and indicates that the changes in the elastic membrane vary widely and are independent of degenerative changes elsewhere. This would seem to corroborate the explanation for degeneration of the elastica as given by Bremer. Because of these wide variations in the status of the elastic membranes of aneurysms that have arisen at bifurcations and from areas of defect in the media of the parent vessel, Forster and Alpers feel that such aneurysms should be considered congenital, regardless of the state of the elastic membrane. The changes in the elastica are secondary to the formation of the aneurysm, and minute classification on the basis of a variable anatomic feature does not seem warranted, particularly when the variability depends on the presence of the aneurysm in the first place.

GUTTMAN, Philadelphia.

LEUCOENCEPHALITIS ASSOCIATED WITH PURULENT LEPTOMENINGITIS (MENINGOLEUCOENCEPHALITIS). I. MARK SCHEINKER, J. Neuropath. & Exper. Neurol. **4**:164 (April) 1945.

Scheinker reports observations in 7 cases of purulent leptomeningitis, in all of which there were widespread, diffuse, inflammatory phenomena involving the leptomeninges and large areas of the central and the subcortical white matter. The lesions in the white matter were inflammatory, hemorrhagic and mixed, with predominance of the inflammatory changes. In some portions of the white matter there were small focal areas of myelin loss, usually seen about small thrombosed veins. The nerve fibers, as well as the glia, were severely damaged or completely destroyed. The gray matter revealed no inflammatory or hemorrhagic changes and appeared fairly well preserved except for a mild degree of edema, associated with diffuse, ischemic alteration of the cells. In cases in which the cerebellum and the spinal cord were examined these changes were inconspicuous.

In the cases reported in this series a pyogenic infection was the primary etiologic feature, with the meningococcus responsible in 4 cases, the pneumococcus in 2 cases and a neisserian diplococcus in 1 case.

Scheinker, in view of the predominant involvement of the white matter and the association of the lesions with purulent leptomeningitis, designates the disorder as a meningoleukoencephalitis.

GUTTMAN, Philadelphia.

STUDIES ON DEVELOPMENTAL PATHOLOGY. III. DISINTEGRATION IN THE NERVOUS SYSTEM OF NORMAL AND MALDEVELOPED EMBRYOS. PETER GRUENWALD, J. Neuropath. & Exper. Neurol. **4**:178 (April) 1945.

Gruenwald reports his observations on changes in microscopic structure in the brain of chick and human embryos which are called "disintegration." Essick originally observed areas in which clefts appear between the cells of the mantle layer in the corpora striata of the human embryo in the second month. In the same area in older embryos cysts were seen which had apparently developed by fusion of the clefts. These cysts are thought to occur in all normal embryos, are not artefacts and disappear completely when the embryo reaches a length of about 24 mm. Hochstetter confirmed and extended Essick's observations. He found that cavities appear again in the corpora striata after the disappearance of those described by Essick. He also observed large cysts in the cerebellum of embryos of 26 to 50 mm. and smaller cysts in the diencephalon. Both authors found similar cysts in some mammals and failed to find them in others.

Gruenwald's studies confirm these observations. His studies show that in certain areas and stages of development of the embryonic brain there are peculiar changes in histologic structure resulting in the formation of clear spaces. Gruenwald calls this phenomenon disintegration and states that in many instances it leads to cyst formation. The changes appear in human and in chick embryos in various derivatives of the forebrain, particularly in the corpora striata and near the ventricular surface of the thalami. Human embryos also show extensive cyst formation in the cerebellum. Gruenwald states that all these changes disappear completely. Similar disintegration and cyst formation were observed in or near malformed parts of the nervous system of chick embryos, in locations where disintegration does not occur normally.

Theoretically, there are several pathologic conditions that may arise from disintegration. In its normal location the disturbance may persist, probably because of an abnormal intensity or extent of the embryonic changes. In abnormal locations disintegration as such is pathologic but may be transitory. It is possible that disintegration may not be permanent but may persist long enough to disturb further development, and it is extremely difficult to predict possible consequences.

The presence of abnormal disintegration in the vicinity of gross malformations indicates that the abnormality extends beyond the gross anatomic disturbance,

either as its sequel or as a primary process. This should be considered in evaluating the extent to which a maldeveloped nervous system may be histologically and functionally disturbed.

GUTTMAN, Philadelphia.

HEAD TRAUMA CAUSING REACTIVATION OF THYROTOXICOSIS, APPEARANCE OF DIABETES MELLITUS, AMENORRHEA AND MELANODERMIA. LUIZ CAPRIGLIONE and JOSE SCHERMANN, Arq. de clin. **1**:311 (Sept.) 1945.

Capriglione and Schermann report the case of a white woman aged 36; the mother had diabetes mellitus and a sibling epilepsy. There was a history of thyrotoxicosis following childbirth ten years previously; this had subsided with conservative treatment. Six months before admission she was in a bus accident and lost consciousness. There was no report of a fracture. Soon afterward, polydipsia, polyuria and vulvar pruitus appeared. She began to lose weight, became nervous, and tremors of the hands appeared. Pigmentary changes were observed. Clinical examination showed an enlarged, nodular thyroid; a small, atrophic uterus and diffuse melanoderma. Her blood pressure was 110 systolic and 70 diastolic in the lying position and 100 systolic and 60 diastolic in the sitting position. The basal metabolic rate was + 22.5 and + 34 per cent on two occasions. The blood sugar measured 250 mg.; the sodium, 350 mg., and the potassium, 25 mg., per hundred cubic centimeters. The blood count was normal. Biopsy of the skin showed abundant melanin pigment in the histiocytes of the skin. Estrogenics in the urine measured 100 and 800 units in twenty-four hours. The authors believe the head trauma caused changes in the diencephalohypophysial region, resulting in exacerbation of thyrotoxicosis due to hypersecretion of thyrotropic hormones. The diabetes mellitus is considered a result of the effect of the hypothyroidism on the pancreas already affected by the previous bout of thyrotoxicosis. The amenorrhea is said to be due to uterine atrophy induced by prolonged hyperthyroidism. The diffuse hyperpigmentation results from stimulation of secretion of intermedin, also a sequel of the head trauma.

SAVITSKY, New York.

Psychiatry and Psychopathology

INSULIN SHOCK TREATMENT AFTER SEVEN YEARS. EARL D. BOND and THURSTON D. RIVERS, Am. J. Psychiat. **101**:62 (July) 1944.

Bond and Rivers reviewed the results of insulin therapy in 251 schizophrenic patients, 138 of whom were recovered or showed improvement at the end of treatment. Forty-nine were followed for five years, and 22 of these maintained their improvement or recovery. The spontaneous recovery rate in a control group was 16 per cent at the end of five years. Of the 138 patients who demonstrated improvement at the last follow-up observation, 88 maintained their status and 25 had had a relapse, which persisted.

Bond and Rivers point out the notably higher rate of recovery in the insulin-treated group than in the control group. They are of the opinion that the quality of the remission in insulin-treated patients is of much higher standard than is the spontaneous recovery.

FORSTER, Philadelphia.

THE EFFECT OF ELECTRIC SHOCK THERAPY UPON CEREBROSPINAL FLUID PRESSURE, PROTEIN AND CELLS. JAMES S. L. JACOBS, Am. J. Psychiat. **101**:110 (July) 1944.

Jacobs studied the alterations in the pressure, protein content and cell count of the cerebrospinal fluid induced with electric shock therapy administered to 21 psychiatric patients. Occasional alterations of pressure were noted, and these

could be correlated with the patient's psychomotor status. Only in 1 patient did the author note a significant alteration in the protein and the cell content. The highest cell count for this patient, who had diabetes, hypertension and arteriosclerosis, was 28 cells per cubic millimeter, and the greatest total protein was 52 mg. per hundred cubic centimeters. Jacobs concludes that the protein and cell contents of the cerebrospinal fluid should be determined prior to administering electric shock to patients with significant arteriosclerosis or hypertensive vascular disease.

FORSTER, Philadelphia.

INSULIN, CARDIAZOL [METRAZOL] AND ELECTROSHOCK TREATMENT IN PALESTINE DURING THE LAST FIVE YEARS. KURT BLUMENTHAL, J. Nerv. & Ment. Dis. **101**:332 (April) 1945.

Blumenthal discusses the theory and rationale of the shock therapies, particularly as applied to schizophrenia. He does not agree with Sakel's belief that the nucleus of the psychosis is being attacked but feels that the hitherto impenetrable wall about the nucleus is being penetrated. He feels that shock therapy "is a brutal and irrational intervention with an attendant therapeutic effect," and that in order to place the procedure on a scientific level the main efforts should be directed toward finding and isolating this therapeutic factor. With insulin shock it is the period of coma which is responsible for the therapeutic effects, and, according to Kuppers, this is caused by the exhaustion of the sugar reserves in the interior of the nerve cells. During the first phase of insulin coma the blood sugar falls, while the intracellular sugar is enriched. At the first "turning point" of Georgi the potential difference has reached its maximum; the cell wall no longer holds, and the intracellular sugar flows through the broken cell walls into the blood stream. The turning point is a phase of enhanced irritability, when the so-called early epileptic seizure may occur. During the second phase the level of the blood sugar is rising while that of the spinal fluid sugar falls, and sugar impoverishment of the brain cells continues. In the metrazol-produced convulsive seizure, similar changes in the sugar content of the blood, spinal fluid and intracellular tissues occur, but in a matter of minutes rather than of hours, as with insulin. The effect of daily insulin coma or convulsive treatments is to increase the permeability of the blood-spinal fluid barrier. If the cause of schizophrenia is presumed to be an unknown toxic agent which causes a reactive "condensation" or decreased penetrability of the blood–brain barrier, then this action of the shock therapies in increasing permeability would be effective in a normalizing manner, since the "condensation" continues after the toxic agent has been eliminated and causes metabolic damage and secondary irreversible damage to the brain.

Of 267 patients with schizophrenia treated since May 1937, 26.43 per cent had full remissions; 28.10 per cent, social remissions, and 25.47 per cent, no benefit. The results were better in patients with early stages of the disease, in those with acute onset and in those with considerable affective component. A combination of insulin coma and convulsive therapy was more successful than either alone, although insulin coma was superior to convulsive therapy. A disadvantage of the convulsive method is the severe loss of memory, which may be responsible for an apparent cure when the patient has actually only temporarily forgotten his delusions.

CHODOFF, Langley Field, Va.

MORBIDITY AND MORTALITY OF PATIENTS WITH PSYCHOSIS DUE TO CEREBRAL ARTERIOSCLEROSIS. O. J. POLLAK, J. Nerv. & Ment. Dis. **102**:27 (July) 1945.

In a series of 2,000 cases in which autopsies were performed at the Taunton State Hospital during the past two decades, the clinical diagnosis of psychosis with cerebral arteriosclerosis had been made in 476. In only one fourth of the latter was death due primarily to arteriosclerosis. The average age at death was 71

years. In contrast to these findings, for other types of mental disease the mortality rate from arteriosclerotic processes was much lower (8 per cent), and, except for the senile psychoses, the average age at death was lower.

CHODOFF, Langley Field, Va.

BRAIN WAVES AND CLINICAL FEATURES IN ARTERIOSCLEROTIC AND SENILE MENTAL PATIENTS. W. T. LIBERSON and C. A. SEGUIN, Psychosom. Med. **7**:30 (Jan.) 1945.

Liberson and Seguin analyzed the clinical symptoms as related to the electroencephalographic pattern in 53 patients with cerebral arteriosclerosis or senile psychosis. The electroencephalographic records were separated into extremely abnormal, intermediate and approximately normal groups. About a third of the patients showed an extremely abnormal pattern, while another third presented no definite abnormality. The patients were then grouped according to their major symptoms, and for each group the percentages of tracings belonging to the various electroencephalographic categories were determined. In the group of patients with highly abnormal records confusion and irritability were more prominent, whereas in the groups with normal and borderline patterns agitation, anxiety and delusions were the most prominent symptoms. Hallucinations and depression showed about the same relative values for the extremely abnormal, intermediate and approximately normal electroencephalographic groups.

WERMUTH, Philadelphia.

BRAIN WAVES AND HEREDITY IN MENTAL DISEASES. W. T. LIBERSON and C. A. SEGUIN, Psychosom. Med. **7**:35 (Jan.) 1945.

Liberson and Seguin studied the importance of hereditary factors in the determination of the electroencephalographic patterns of 118 patients with mental disease between 13 and 23 years of age. The electroencephalograms were classified according to the degree and kind of abnormality present, and the patients were grouped according to the presence and importance of the abnormal hereditary factors in the family history. The authors found relatively more patients with normal electroencephalograms in the group with a negative family history for mental disease than in the group with a positive history.

WERMUTH, Philadelphia.

DIFFERENCE IN THE MENTAL REACTION BETWEEN CHILDREN SUFFERING FROM CEREBRAL AND CEREBELLAR TUMORS. LEO M. DAVIDOFF, Psychosom. Med. **7**:38 (Jan.) 1945.

Davidoff, over a period of twenty years, observed that children with tumors of the cerebellum seem to be unusually alert and cooperative and to have sweet dispositions. A review of hospital records of about 50 children with cerebellar tumor appeared to bear out this impression. A group of 20 children with supratentorial tumors, on the other hand, behaved in the manner usually expected of severely sick children.

WERMUTH, Philadelphia.

THE RELATIONSHIP OF ANTI-SOCIAL TRAITS TO THE ELECTROENCEPHALOGRAM IN CHILDREN WITH BEHAVIOR DISORDERS. JOSEPH J. MICHAELS, Psychosom. Med. **7**:41 (Jan.) 1945.

Michaels found a high incidence of stealing and sexual misbehavior in a series of 122 children with behavior disorders. Enuresis was associated in a positive manner with all the antisocial traits. Analysis of the electroencephalograms of these children revealed that fire setting was the only sociopathic trait that was associated in a positive manner with electroencephalographic abnormality. Enuresis, a psychobiopathic trait, also was positively associated with the abnormal electroencephalogram.

WERMUTH, Philadelphia.

RESULTS OF SHOCK THERAPY EVALUATED BY ESTIMATING CHANCES OF PATIENTS REMAINING IN HOSPITAL WITHOUT SUCH TREATMENT. L. S. PENROSE and W. B. MARR, J. Ment. Sc. **89**:374 1943.

Penrose and Marr described a new statistical method in shock therapy, the essence of which is a comparison of the actual number of shock-treated (insulin, metrazol) patients remaining on the hospital books at a given time with the expected number calculated from a random sample of the mental hospital population. Discharge, rather than probation, was taken as the index for the comparison of treated and control patients. The two groups were matched according to sex, age on first admission and lapse of time since the first admission. There is clear indication that fewer shock-treated patients remain on the hospital books than are to be expected from considerations of the control sample. An improvement attributable to shock treatment in the patients' conditions is implied; this is slight in cases of schizophrenia but pronounced in cases of manic-depressive and involutional psychosis.

KATZ, Boston.

Treatment, Neurosurgery

RECONSTRUCTION OF THE FACIAL NERVE. A. C. FURSTENBERG, Arch. Otolaryng. **41**:42 (Jan.) 1945.

Furstenberg believes that the facial nerve should be preserved in operations on the parotid gland. It is possible and practicable to remove the entire parotid gland with preservation of the critical fibers of the seventh nerve. Careful and painstaking delineation of the nerve fibers, which may be identified with a light faradic current, frequently leads to excellent results. Removal of an infiltrating tumor of the parotid gland is compatible with preservation of the nerve. An optimistic point of view with regard to safeguarding the nerve can best be maintained by an initial exposure of the trunk near its emergence from the stylomastoid foramen. Thus early identification of the nerve is made possible, and its important ramifications may be traced with facility throughout the parotid gland.

In cases of traumatic injuries of the facial nerve an end to end anastomosis should be used when practicable. This is predicated on the assumption that the nerve has been severed by a clean cut or that only a small part of it has been damaged. Grafting may be the only method possible when large portions of the facial nerve have been destroyed. This entails, however, two points of union and thus doubles the hazard of fibrous connective tissue encroaching on the joints. In carrying out end to end anastomosis, the tortuous route of the facial nerve can be appreciably shortened by lifting the nerve out of its bony canal and freeing it along its course in the parotid gland. A union of the ends of a severed nerve which at first seemed futile may often be accomplished with this method.

RYAN, Philadelphia.

EARLY REPAIR OF NEURAL WOUNDS WITH PENICILLIN THERAPY. NATHAN C. NORCROSS, Arch. Surg. **50**:67 (Feb.) 1945.

War injuries of peripheral nerves should be repaired as early as possible in order to obtain a good functional result. This can be successfully accomplished with the help of penicillin therapy. Patients with apparently clean wounds were given 10,000 units of penicillin every three hours from the second preoperative to the eighth postoperative day. To patients with infected wounds 20,000 units of penicillin was administered every three hours from the fourth preoperative to the tenth postoperative day, or longer. In all cases the wounds healed by first intention without complications.

LIST, Ann Arbor, Mich.

PENICILLIN TREATMENT OF NEUROSYPHILIS. A. S. ROSE, Connecticut M. J. **9**:522 (July) 1945.

During the past fourteen months the neurosyphilis service of the Boston Psychopathic Hospital has treated 140 patients with symptomatic neurosyphilis. The treatment consisted of one half the usually prescribed amount of fever therapy and injections of penicillin, given concurrently or in succession. Sodium penicillin dissolved in saline solution was administered intramuscularly for a total dose of 3,000,000 Oxford units. According to Rose, penicillin is an active therapeutic agent in all forms of neurosyphilis, but the degree of effectiveness has not been determined. The best results are obtained with syphilitic meningitis. A small series of patients with primary optic nerve atrophy have shown surprisingly good results. All forms of parenchymatous neurosyphilis apparently need fever therapy as well as penicillin. Penicillin is an agent which acts directly on the invading organisms and therefore can be useful only in cases in which there is evidence of spirochetal activity.

J. A. M. A.

INJURIES TO THE CENTRAL NERVOUS SYSTEM. WINCHELL MCKENDREE CRAIG, J. Nerv. & Ment. Dis. **101**:451 (May) 1945.

The treatment of closed and open injuries to the head has been improved since the effect of anoxia produced by trauma and inadequate breathing has been understood and a clear airway provided by placing the patient in the prone position, so that the tongue may fall forward and the saliva and vomitus escape. The use of oxygen not only has relieved anoxia but has helped to reduce increased intracranial pressure. Cerebral edema has been combated by the administration of plasma and serum albumin.

In this war infected head wounds have been a rarity, owing to the use of sulfonamide drugs and penicillin. Careful surgical débridement has been aided by the use of electrocoagulation and suction, and hemostasis, by the use of fibrin foam. The repair of defects in the skull with autogenous bone or cartilage or with alloplastic materials, such as vitallium, lucite or tantalum, has been much improved.

CHODOFF, Langley Field, Va.

ELECTROCONVULSIVE THERAPY OF ACUTE HYSTERIA. FRED FELDMAN, SAMUEL SUSSELMAN, BASILE LIPETZ and S. EUGENE BARRERA, J. Nerv. & Ment. Dis. **102**:498 (Nov.) 1945.

The authors report 2 cases with acute hysterical manifestations in which the results of electric shock therapy were successful. The first case was that of a white woman aged 29 who had generalized tremors and inability to walk following an automobile accident eighty-five days previous to admission. She failed to improve significantly after eight sodium amytal interviews and exhibited a new symptom—belching of air. Electroconvulsive thtrapy was instituted, and the patient showed rapid improvement and was discharged after nine treatments. The second case was that of an amnesic young woman, who also failed to respond to sodium amytal narcoanalysis. On the fourth hospital day she was given an electrically induced convulsion, which was followed within five minutes by the beginning of progressive improvement of memory.

CHODOFF, Langley Field, Va.

COMPOUND CRANIOCEREBRAL INJURIES. W. J. GERMAN, B. S. BRODY, and S. C. HARVEY, Surgery **16**:874, 1944.

German, Brody and Harvey reviewed a series of 64 cases of compound craniocerebral injuries. Sixty of the patients were operated on; the remaining four died within one and a half hours of admission, before preparations for operation could be

completed. The general policy of therapy was as follows: (1) immediate treatment of shock; (2) inspection, but not palpation, of the wound; (3) roentgenographic examination to reveal the extent and type of the fracture, and (4) operation within six hours for all patients surviving a preparatory period of two hours. The surgical principles employed were: (1) local anesthesia; (2) thorough débridement of the scalp, cranial wound and devitalized brain tissue; (3) removal of in-driven fragments of bone and foreign bodies; (4) closure of the dura, if possible, and (5) tight closure of the scalp. All patients (14 per cent) over 60 years of age died, their deaths forming more than 50 per cent of the mortalities in the series. Coma was generally a grave prognostic sign; nevertheless, more than one-third the patients arriving in deep coma survived. It does not seem that one is warranted in delaying operation for several hours in order to assess better the chances of the patient, at the same time increasing the possibilities of infection by delay. The authors agree, however, that when large numbers of battle casualties require urgent treatment the state of consciousness should be an important factor in selecting those with the more favorable outlook for early operation.

Shock should rarely delay operation beyond six hours, since modern methods of shock therapy are so effective and only the most severely injured will fail to respond in this time.

Operation was begun within six hours after the injury on all but 2 patients. Block removal of the compound scalp and cranial wound was done in 19 of the 52 patients whose wounds were not due to projectiles. The operative mortality rate was 26 per cent. This included the most severely injured patients. Excision of the scalp wound and removal of fragments from the cranial wound were done in 20 patients, including those with orbitonasal injuries, with an operative mortality of 10 per cent. Débridement of the scalp wound without removal of bone, chiefly for linear fractures without bone depression, was done in 13 patients, with an operative mortality of 7.7 per cent. The over-all operative mortality for those patients (52) without wounds due to projectiles was 15.4 per cent, and one-half these deaths were in patients over 60 years of age.

Primary closure of the scalp was done on all patients. Drains were inserted in the wounds of 29 of the 60 patients operated on. The dura was closed whenever possible.

In only 2 of 51 patients surviving six days did severe infections develop, and of these 2 patients, 1 died, a mortality due to infection of 2 per cent. Seven patients (14 per cent) had infections of the scalp, and only 2 of these occurred in persons for whom drainage had not been employed.

Nine patients had injuries due to missiles, and 6 of these (66.7 per cent) died. One of them died before operation could be performed. All 4 patients with traversing wounds died after operation. The total mortality rate for the entire series of 64 patients was 26.5 per cent, and the over-all operative mortality was 21.6 per cent.

SHENKIN, Philadelphia.

ELECTROCOAGULATION OF GASSERIAN GANGLION. K. H. BAUER, Chirurg **16**:1 (Jan.) 1944.

Bauer reports experiences with electrocoagulation of the gasserian ganglion in more than 500 cases of neuralgia. There was not a single fatality. Injection of solution of procaine hydrochloride is made to infiltrate the track for the puncture cannula to the base of the skull. A 12 cm. long, thin cannula, insulated with pyroxylin, is introduced and is passed slowly forward along the foramen ovale without touching the base. The passage through the foramen ovale is made manifest by sudden, radiating pain in the area of the third branch and by resistance offered by the nerve. Roentgenographic examination of the position of the needle prior to coagulation is imperative. Examination of the eyes is important because changes in vision, in the size of the pupils and in the ocular movements suggest that a change in the position of the needle is required. This may also be necessi-

tated by aspiration of blood or cerebrospinal fluid or by nausea. After these precautionary measures, high frequency electrocoagulation with the alternating current may be performed with the patient under evipal sodium anesthesia. Coagulation should be made in four stages, of fifteen, twenty, twenty-five and thirty seconds' duration. The intensity of the current is increased during the last stage. Coagulation itself should not be performed with local anesthesia. Residual pains may persist for two or three days. Electrocoagulation may be repeated when pain persists on the fifth or sixth day, as well as when there are recurrences. The advantage of the method is that the effect of the current is limited to the area immediately next the cannula, thus preventing severe destruction at the base of the skull or extensive sequestration of bone in the area of the base and of the upper jaw.

J. A. M. A.

ELECTROCOAGULATION OF GASSERIAN GANGLION BY THE KIRSCHNER METHOD. B. ODDSSON, Acta psychiat. et neurol. **19**:293, 1944.

In the neurosurgical department of Rigshospitalet, in Copenhagen, 86 patients with trigeminal neuralgia have been treated during the last six years with electrocoagulation of the gasserian ganglion by the Kirschner method. The location of the foramen ovale having been found percutaneously with an apparatus specially designed by Kirschner, the ganglion is punctured with a trocar; the stylet is removed, and a cautery probe is introduced, with which the ganglion is electrocoagulated. The operation takes a few minutes. The patients were between the ages of 19 and 92. There were 54 women and 32 men. The average duration of the neuralgia was six years, the longest period being thirty years and the shortest three months. The right side was affected in 55 patients and the left in 28 patients, and 3 patients had bilateral neuralgia; 74 patients had major and 12 atypical trigeminal neuralgia. Sixty-six patients had primary relief of symptoms, the remaining 20 having to undergo other treatment. The longest follow-up observation was fifty-one months; the shortest, three months. The follow-up observation revealed that 25 patients were relieved of pain and 7 were substantially improved; 13 patients had a recurrence, which in most cases yielded to a repeated electrocoagulation. There were no deaths. The best results, both as to primary relief of symptoms and as to prevention of recurrence, were obtained with trigeminal neuralgia of the third division. Oddsson suggests that most patients with major trigeminal neuralgia should be treated with temporal retrogasserian neurotomy. If the patient is not likely to stand the operation, injection of alcohol or neurexeresis may be carried out if the first and second divisions are involved, while with neuralgia of the third, and perhaps also of the second, division electrocoagulation of Kirschner should be performed. In special cases section of the sensory root alongside the pons by Dandy's subcerebellar route may be considered, but it seems likely that this operation will be superseded by the tractotomy of Sjöqvist, which has definite advantages.

J. A. M. A.

Society Transactions

PHILADELPHIA NEUROLOGICAL SOCIETY

Walter Freeman, M.D., Presiding

Regular Meeting, Oct. 26, 1945

Experimental Observations on the Use of Stainless Steel for Cranioplasty: A Comparison with Tantalum. Dr. Michael Scott and Dr. Henry T. Wycis.

Stainless steel was used for cranial defects in 3 dogs, which were killed at the end of six weeks, three months and six months, respectively. The gross and microscopic studies made on these dogs showed that the stainless steel plates were completely encapsulated in every instance. There was no evidence of infiltration with polymorphonuclear leukocytes or round cells in any of the sections. There was no collection of serum above or below the plates. The reaction following the insertion of a stainless steel plate in the subdural space compared favorably with that reported by Pudenz and Odom following insertion of a tantalum plate in the subdural space.

Stainless steel plates were used in repair of cranial defects in 3 patients, but the follow-up period had been too short to warrant any conclusions.

It was concluded that the stainless steel plates compared favorably with tantalum plates used in similar locations. Stainless steel plates are easily obtainable and can be cut, shaped and molded at the operating table, and the price is approximately one-two-hundred-ninetieth that of tantalum. The authors believe that this material should be given a thorough clinical trial.

DISCUSSION

Dr. Rudolph Jaeger: The problem of cranioplasty would seem at first glance to be a rather simple one. There is a hole in the skull, and it is to be filled with something or other. One would think one could take bone from here or there, or almost any noncorrosive metal that is not irritating, and fill the opening without the need for profound thought on the matter.

It is evident from a review of the surgical literature that cranioplasty must present a weighty problem in neurosurgical technic, because a great deal of thought has been applied to this procedure. I have felt that perhaps one single material should not be used exclusively for such repairs. The mental stability of the patient should be seriously considered when closing a defect in the skull. An older person whose mental reactions are well established will tolerate mentally almost any material one may wish to put into the skull. With the more nervous type of person, particularly one who has a tendency to a neurosis, one must think twice before putting a material like metal into a defect in the skull, where it will always show up in the roentgenogram. Almost certainly the patient will learn that it is there, and he may react mentally against its presence. I have felt that with this type of patient it is better to fill the defect with bone if it is possible. Once in a while the opening is so large one cannot find bone enough and must resort to metal or to Plexiglas.

Some years ago I started using stainless steel, soon after it was first advocated as a suturing material. I have closed a number of skull defects with it since. I have followed the patients for a number of years, and in no instance have I found any signs of irritation or tendency to extrusion of the plate. I have used stainless steel many times in wiring the bone flap and in opening the wound for a second operation have seen the bright shining wire without any tissue irritation

around it. That is quite different from the reaction observed around a silver clip, where there is a blackened area of fibrosis, due to the oxidation and discoloration of the tissues.

I should like to mention 2 cases in which stainless steel was used for cranioplastic closure which are of importance in illustrating the tolerance of the cranial tissues to this substance. In the first case a large bone defect remained in the frontal part of the skull after the removal of a huge area of hyperostosis and an underlying meningioma. This was filled by a stainless steel plate, perforated many times and measuring 13 by 11 cm. Six years later there were no signs of irritation from it, and the cosmetic result was excellent. In the second case roentgenographic examinations and observations were made at frequent intervals for seven years. This steel plate was much smaller (2 inches [5 cm.] in diameter). There has not been the least sign of irritation from it.

While I prefer closing defects of the skull with tibial grafts wherever possible, I can see no reason that stainless steel is not fully as good as tantalum or other metals for this purpose.

DR. HENRY T. WYCIS: I want to thank Dr. Jaeger for presenting these cases, because it gives one a little more confidence in knowing that one can leave these stainless steel plates in the skull for a long time without any untoward result.

It is of interest that no matter what is put in the skull, particularly in the epidural space, one can hardly escape getting a reaction around it. It is evident that all these plates were surrounded by a capsule, even though wired in the epidural space; so the plate certainly reacts as a foreign body.

The Adult or Late Form of Amaurotic Idiocy. DR. N. W. WINKELMAN.

An Irishman aged 25, with a history of convulsions from the age of 17, was brought to the hospital in status epilepticus. He was confused and maniacal. His temperature began to rise, and death occurred four days after his admission.

Pathologically no gross lesions were encountered. Histopathologic examination disclosed cells typical of amaurotic idiocy (the so-called Schaffer cell process), in groups or singly, scattered throughout the entire cerebrum, but especially in the cornu ammonis and the subthalamic area. In the few cases reported in the literature the cerebellum has been particularly involved, and the spinal cord to much lesser degree.

No well defined clinical syndrome can be given in view of the wide variability of the clinical pictures in the few cases reported.

The age of onset of the condition, the clinical picture, which does not fit into any of the three types previously described, and the presence of the ballooned-out cells of the Schaffer type, singly or in groups, throughout the entire nervous system, but especially in the cornu ammonis and the subthalamus, justifies the placing of this case into the most recent subdivision of amaurotic idiocy established by Kufs and called by him the adult form of that disease.

DISCUSSION

DR. JOSEPH YASKIN: What areas showed the late pathologic changes?

DR. GEORGE D. GAMMON: What does autopsy show in other organs in the body in these late cases of amaurotic idiocy? Has there been any infiltration of fat elsewhere, as in the liver or spleen?

DR. FREDERIC H. LEAVITT: I believe the infantile form is supposed to be more prevalent in certain types of people. Is this condition looked on as a developmental defect, a degeneration or a possible infectious state?

DR. N. W. WINKELMAN: In answer to Dr. Yaskin's question as to the location of the process: While it was widespread and irregular, it involved the cornu ammonis and the subthalamic area to a greater degree than the rest of the central nervous system.

In answer to Dr. Gammon's question: A complete study of the organs of the body failed to disclose any unusual changes, although in Kuf's second case a marked terminal disturbance of the lipid metabolism was observed in all organs.

As to Dr. Leavitt's question, I want to stress that at no point was there even a suggestion of an inflammatory process. It is likely that the process is a heredodegenerative one, as Schaffer himself interpreted the condition. It is to be emphasized that the first reports of Kufs described the same condition in a sister and brother. The twin brother of my patient, who died in infancy of a cerebral condition, may have had a similar condition. Unfortunately, no autopsy was done.

From the report by Kufs, it is likely that these cases also belong to that group in which disorders of lipid metabolism have been found.

Robert A. Groff, M.D., *Presiding*

Regular Meeting, Feb. 22, 1946

Vital Staining of Experimental Brain Abscesses. Dr. Philip P. Goland (by invitation), Dr. Henry A. Sloviter (by invitation) and Dr. Francis C. Grant.

It has previously been demonstrated that when injected intravenously basic dyes stain the intact brain, whereas acid dyes, such as trypan blue, do not stain the uninjured brain. A number of workers have shown that when an acid dye is injected into an animal whose brain has been injured the dye tends to accumulate around the site of the lesion because of the local breakdown of the blood-brain barrier, whereas the remainder of the brain remains unstained.

In the present work, several azo and triarylmethyl dyes were synthesized and tested. One of these, an acid monazo dye, gave good staining and had the necessary requirements of low toxicity, good color stability, solubility and ready elimination. This new dye is the sodium salt of *p*-bromobenzene-azo-2-naphthol-3, 6-disulfonic acid.

The technic used for the production of brain abscesses in dogs was essentially that of Markley (*Proc. Soc. Exper. Biol. & Med.* **47**:171, 1941). The best results were obtained by operation in the frontal region. Two days after injection of bacteria, 0.1 Gm. of dye per kilogram of body weight was injected intravenously as a solution in 5 per cent dextrose. In most cases a second, similar, dose was administered after one or more days.

Postmortem examination of the brains of 26 dogs so treated revealed the following conditions: 1. In 13 brains acute abscesses developed, and 11 of these showed definite staining of the region surrounding the abscess. The grossly necrotic brain and the brain with acute encephalitis showed staining; the pus in the abscesses did not seem stained. 2. Six brains showed agar plugs with minimal reaction, and 5 of these were stained. 3. In 3 brains ventriculitis developed and in all the ventricular walls were stained. 4. In 4 brains meningitis developed, and no staining of pus or the leptomeninges was obtained. In no case was staining of the uninjured portions of the brain observed. Color photographs of some of the brains containing stained abscesses were shown.

Since the dye described contains a bromine atom, it is possible that introduction of a radioactive isotope of bromine may make it useful as a radioactive tracer. Further investigation of this possibility is now being made.

DISCUSSION

Dr. Francis C. Grant: The possible importance of the results that Dr. Sloviter and Dr. Goland have obtained lies in the possibility that these findings may facilitate the localization of a cerebral abscess. The selective staining of an infectious process might greatly improve the chances of its accurate identification

after exposure of the suspected area. There is much work yet to be done, including of course the all-important first step of determining the toxicity of this material in man.

DR. BERNARD J. ALPERS: This is an interesting paper. There is just one question that I should like to ask in relation to this study. It is known that if a vital dye is injected into the area of damage to the brain the dye is taken up by microglia cells particularly. This has been shown in an effort to determine whether the microglia cells were a part of the reticuloendothelial system.

It seems to me that the injection in the brains reported must be indicative of destruction of the brain tissue caused by the original experimental procedure and that it may have nothing to do with the process of the brain abscess itself. I wonder whether the authors have any observations on the type of cells that take up this dye. If it is the microglia cells, these observations would have relatively little application to the human brain, for the infiltration around cerebral abscesses is hematogenous.

DR. PHILIP P. GOLAND: We have been going over the sections with Dr. N. W. Winkelman, and we have not as yet determined which type of cell takes up the dye. We are going to make sections in which we do not use counterstains, such as hematoxylin and eosin. We are going to mount some sections unstained and see whether we can find particulate dye matter in them.

In connection with infections outside the brain there have been some studies with dyestuffs, and it has been shown that cells of the granulomatous reaction types will hold certain vital dyes. Macrophages and fibroblasts pick up these dyes, and the dye can be seen within these cells in granular form. The macrophages have a greater power of storing vital dyestuffs, but these deposits are less permanent than the more minute deposits in the fibroblast cells. It is possible that in chronic abscesses of the brain the fibroblasts may pick up the dye and hold on to it for a long time.

Reversibility of Dilatation of Cerebral Ventricles. DR. HENRY A. SHENKIN and DR. CHARLES R. PERRYMAN.

Three cases were reported of internal hydrocephalus caused by an obstructing lesion in either the third or the fourth ventricle which had been studied ventriculographically before and after relief of the obstruction. In every case the lateral ventricles were smaller after operation. It is believed that ventricular size is reversible in many instances if the dilatation of the ventricles is due to an obstructive lesion and the obstruction has not been present too long.

DISCUSSION

DR. ROBERT A. GROFF: The data presented by Dr. Shenkin are very interesting. I was of the opinion that after relief of intracranial pressure, especially that resulting from tumors of the posterior fossa, the ventricles tend to return to a relatively normal size. These studies seem to bear out this opinion, or at least to show that the dilatation does not continue.

Two questions came to my mind during the presentation. Were the fluid contents of the ventricular system compared in the two examinations made on each of the patients? Why was a ventriculoencephalographic examination done as the second procedure on 2 of the patients since it does not permit a true comparison?

DR. JOSEPH C. YASKIN: I am not sure, Dr. Groff, whether the findings in air studies can be regarded as conclusive proof of either the relative size of the ventricles or of cerebral atrophy. I believe that it is open to doubt in this case even though Dr. Shenkin used accurate, comparable technics with respect to the amount of fluid withdrawn and air introduced, the exposure, etc. Moreover, a study of 3 cases, even though absolutely accurate, is not completely convincing as to reversibility.

DR. CHARLES R. PERRYMAN: I am not sure whether it was Northfield who in studies on cadavers pumped large amounts of air into the ventricles and was not able to demonstrate a sufficient change in the size of the ventricles to make distention a significant factor. This, of course, was in the cadaver, and not in the living patient. The neurophysiologic aspect is probably the most interesting, and we did not consider it in our discussion. One wonders whether this enlargement of the ventricles, if it is not due to atrophy, could be the result of decreased fluid volume in the brain. In other words, is there less subarachnoid fluid and a smaller blood volume, or is some other factor responsible?

DR. BERNARD J. ALPERS: Is there any relationship between the duration of the hydrocephalus and the process of reversibility? Is it more likely that there will be reversibility when the hydrocephalus is acute than when it is chronic? Also, what is the functional interpretation of decrease in the size of the ventricle? Decrease in size of the ventricle need not indicate that function of the brain will improve, for good cerebral function is not incompatible with hydrocephalus. It is seen with hydrocephalus of rather extreme degrees.

DR. H. T. WYCIS: I merely wish to call Dr. Shenkin's attention to a report in 1943 by Dr. Jefferson Browder. Dr. Browder had shown a similar reversibility of dilatation of the cerebral ventricles following operation for subdural hematoma.

DR. HENRY A. SHENKIN: The duration of the symptoms in all 3 cases was short. Onset preceded admission to the hospital by two to three months. The tumors were all rapid growing.

In the second case, in which there was the least reduction in size of the ventricles, the postoperative air study was done three months after operation, whereas in the first case it was done fourteen months after operation. Another factor which may explain the difference in the degree of return to normal ventricular size is the age of the patient. Our oldest patient, aged 38, showed less recovery than the other 2 patients, aged 8 and 18 years, respectively.

The fluid was measured in each instance, but usually the initial study was ventriculographic and the follow-up study ventriculoencephalographic. The amounts of fluid obtained, therefore, from the preoperative and the postoperative study were not comparable.

Enlargement of the ventricular system with normal intracranial pressure is not infrequently found after cranial trauma. It has been suggested that this is due to focal cerebral edema at the time of the injury, which causes a tentorial pressure cone and resultant block of the aqueduct of Sylvius, leading to internal hydrocephalus. The ventricles are said to remain enlarged even after the causative mechanism has disappeared.

Certainly, with the cases that we have shown tonight, this theory should be placed in some doubt, and other, more basic, changes in the cerebral hemispheres should be considered.

Effects of Denervation on Fasciculations in Human Muscle and Relationship Between Fibrillations and Fasciculations. DR. FRANCIS M. FORSTER, DR. BERNARD J. ALPERS and DR. WINSLOW J. BORKOWSKI (by invitation).

This article will appear in a future issue of the ARCHIVES.

DISCUSSION

DR. RICHARD MASLAND, Philadelphia: It is important to emphasize the distinction between fibrillation and fasciculation. In fibrillation the individual muscle fibers contract independently. In fasciculation there is a synchronized discharge of a group of muscle fibers. There is every reason to believe that this synchronization is due to neural activity and represents the response of a motor unit to a nerve impulse.

It has been shown that in the case of the fascicular twitch which follows the administration of neostigmine there is a nerve impulse associated with the contraction. This impulse may arise either through antidromic musculoneural trans-

mission or by direct stimulation of the nerve ending sensitized by the drug (Eccles, J. C.; Katz, B., and Kuffler, S. W.: *J. Neurophysiol.* **5**:211, 1942). When the nerve ending is stimulated, an antidromic impulse is set up; there is an axon reflex, and a motor unit discharge results.

There is a striking similarity between the "neostigmine twitch" and the fasciculation of anterior horn cell disease. Both are inhibited by small doses of curare. The experiments just concluded indicate that each arises at the nerve ending. It is my belief that in each instance the fundamental element is an abnormal excitability of the nerve ending.

In attempting to explain the fact just demonstrated that although the disease is in the anterior horn cell the twitch arises at the nerve ending, it is important to bear in mind that the anterior horn cell includes not only the cell body but the peripheral nerve, which is its axon, and the nerve ending. It is not remarkable, therefore, to discover that a disease which is demonstrated pathologically in the cell body within the spinal cord produces striking physiologic changes in the entire cell. These manifest themselves as an alteration in excitability at one of the more highly specialized portions of the neuron—the nerve ending.

Dr. Bernard J. Alpers, Philadelphia: I should like to say something in regard to the clinical significance of muscle fasciculations. A sharp, cleancut distinction must be drawn between the physiologic origin of fasciculations and their clinical significance. Physiologically, it seems to be true that the fasciculations occur as a result of some mechanism taking place at the myoneural junction.

Dr. Masland mentioned sensitization at the myoneural junction. I should like to know what he means by sensitization, for it has been thought that fasciculations are fired off as a result of sensitization to acetylcholine. All things considered, the evidence indicates that the physiologic mechanisms, whatever they are, take place at the myoneural junction, but one is still left with the clinical significance of fasciculations. From this standpoint it seems still to be true that they are indicative of anterior horn cell disease. We have made a number of observations on other patients with other conditions. Fasciculations were found in a patient with severe disease of the cauda equina but not in another patient with a similar lesion. They were also seen with serum neuritis and with ischemic neuritis. In these conditions either there is associated anterior horn cell disease or the fasciculations may represent the result of retrograde changes in the anterior horn cell. Fasciculations may occur in diseases other than those involving the anterior horn cell, but in my opinion many of the diseases which are reported as occurring with fasciculations without involvement of the anterior horn are in fact found to be associated with anterior horn cell disease. This is true of infectious polyneuritis, which is said to occur with fasciculations very frequently, as well as of serum neuritis.

I should like to raise the question of the significance of fasciculations in acute peripheral nerve disease. May these not be the result of associated anterior horn cell disease?

Dr. Richard Masland, Philadelphia: In reply to Dr. Alper's question, Eccles has expressed the opinion that the increased irritability of the nerve ending observed with neostigmine poisoning may be due to prolonged negativity. In view of the striking similarity between the twitch seen with such diseases as amyotrophic lateral sclerosis and the "neostigmine twitch," it is not unreasonable to postulate that the same factor is responsible for both.

Dr. Frederic H. Lewey, Philadelphia: The question of fibrillations or fasciculations is important also from the clinical point of view. A review of the textbooks shows it to be almost an axiom that "fibrillation" is characteristic of a lesion of the anterior horn cell, in contrast to one of the peripheral nerve. Oscillographic records show that the completely denervated muscle "fibrillates." This is not visible clinically. The first sign of beginning reinnervation of a muscle is the appearance of not yet synchronized, spread potentials, which are now called "fasciculations"! They are visible clinically as what were formerly called fibril-

lations. No voluntary motion is possible at that stage. The last stage of muscle reinnervation is characterized by the appearance of synchronized action potentials, i. e., spikes, accompanied with the return of voluntary movements. This experience gained from patients with peripheral nerve injuries corresponds to the observations of the authors, with the restriction that in diseases such as spinal progressive muscular dystrophy some units may be diseased and others still functioning well.

DR. FRANCIS M. FORSTER, Philadelphia: Our use of the term anterior horn cell should be clarified, for by that term we referred to the cell body and its nucleus, and not specifically to the axonal terminations. The experimental data presented this evening indicate definitely that the impulses giving rise to fasciculations did not originate from the portions of the cells in the ventral horns of the spinal cord. Fundamentally, I do not believe there is any real difference of opinion between ourselves and Dr. Masland. Our studies did not include patients with myopathies. However, the myopathies are not always sharply delineated, and the occurrence of clinical or pathologic evidence of involvement of the cord with the myopathies is by no means rare.

PHILADELPHIA PSYCHIATRIC SOCIETY

O. Spurgeon English, M.D., *President, in the Chair*

Regular Meeting, Nov. 9, 1945

The Thematic Apperception Test: Its Value in Routine Psychiatric Practice. DR. HERBERT FREED, in collaboration with DR. W. F. ECCKER.

The thematic apperception test is one of the projective technics. Whereas the Rorschach test has perhaps been the one of this group of tests most utilized, the thematic apperception test has a distinct advantage when one wishes to determine the content of a psychiatric disturbance rather than its form. For this reason it can be used to facilitate therapy, since it often gives an immediate insight into the psychodynamics of the personality.

The defects of the test were discussed, as well as its advantages, and 3 cases were used as illustrations.

DISCUSSION

DR. W. F. ECCKER: As a means of research, the patients were tested without the examiner's being familiar with their case records, in order to find out how well the test can determine features of the personality under evaluation. Usually the test is carried out after some information about the patient is obtained; and the more one knows about the patient the more one can find out. As a matter of fact, when the psychiatrist wants to find out anything specific about the patient, he indicates what he is seeking to the one administering the thematic apperception test.

DR. GERALD H. J. PEARSON: This test is a good supplement and complement to the Rorschach test. I suppose most psychiatrists of my generation at least are somewhat skeptical about tests as means of evaluating personality. This skepticism is not entirely justified, as this test proves. The diagnosis of the depth of the patient's illness cannot be made from the Rorschach test, whereas an evaluation of the content of his conflicts can be made with the thematic apperception test. Thus one test complements the other.

This test is useful in the diagnosis when time is limited, particularly in clinic work, or when a diagnosis has to be made rather quickly. Some time ago I examined a number of children from an orphanage. Orphanage children, particularly children who have been brought up from very early childhood in an institution, have a particular type of personality, which Anna Freud has described in her recent book, "Children Without Families." They have made

a good superficial adjustment. They get along well with other people, are bland, easy to manage, show little emotional reaction and say little about themselves. These children were all given a Rorschach and a thematic apperception test, and, as a result of the testing, it was found that a number who were apparently getting along nicely were actually extremely sick. These results show that if a rapid diagnosis is needed one can get a great deal of help from the thematic apperception test and the Rorschach test. Dr. Freed quoted Murray as saying that this test might be useful in psychotherapy. Anything that will help in getting significant material about the patient early is undoubtedly of value. Nevertheless, I see one or two dangers. If a psychiatrist gives the thematic apperception test in the beginning of psychotherapy and gets certain impressions about the patient from the test, he may tend, unless he is careful, to force the patient to produce material in psychotherapy which will substantiate the results of the test. Also, because he knows certain facts about the patient, he may tend to watch only for those facts and forget, or perhaps lose sight of, other intrapsychic currents of equal importance.

DR. MAX ROSSMAN, Allentown, Pa.: From the way in which the material was presented, I felt that the thematic apperception test is a psychiatric technical tool rather than a psychologic test, such as an intelligence test. The thematic apperception test can be interpreted from three aspects—the literary quality, the emotional evaluation and the themes. From a diagnostic point of view, some awareness of the dynamics of the illness, of defense reactions and of emotional tone can be achieved by utilizing the thematic apperception test.

DR. H. CRAIG BELL: Could Dr. Freed tell us something about the technic of giving the test?

DR. WILLIAM FRANKLIN ECCKER: To determine the intelligence from the thematic apperception test is not an accurate procedure, but after the psychologist has given several thousand intelligence tests he can judge pretty well from the responses of the patient, from his handling of the vernacular and from his other behavior. However, this is not so reliable a way of getting some measure of the intelligence as is a regular intelligence test.

As for a description of the test, there are 30 cards. Ten cards are usually administered to men only, 10 to women only and 10 are given to both sexes. More recent developments in the test also include cards that can be given to children. It usually takes the patient about five minutes to make a story of two or three hundred words for one card; the entire test takes about an hour. If the examiner goes too far over the hour, the patient becomes tired, and the responses are not so reliable. Also, during the first hour the examiner gets acquainted with the patient. After he once has the patient's confidence, he can elicit much more material in the subsequent batch of 10 cards, which part of the test is carried out a few days later.

The cards are mostly of people. Most of them are of characters with whom the patient can identify himself. Some cards are of older persons, which the patient uses to identify with one or the other of his parents; and on other cards there are pictures which he can identify with other persons around him.

With regard to Dr. Rossman's comment, the test is a new one. It has not yet seen the development of the Rorschach test. Dr. Murray first published it in 1935, and it has not been subjected to much research, nor has it yet been standardized. The scoring procedure is not as complicated as that of the Rorschach test.

DR. HERBERT FREED: Something can be done in the way of diagnosis. We hinted at it in the paper. It will be found that one can often make a diagnosis of hysteria from the way the patient words her stories. Again, patients with compulsive neuroses will often not come to any one conclusion as to what the character does; their indecision in telling the story may become diagnostic. The same holds true with schizophrenia.

Perhaps I am too optimistic, but I think that in the future we shall have a different type of diagnostic classification. One will not depend on a label

and say that this patient has schizophrenia but will say that he has certain dynamic trends which underlie his illness. I think this test will have a great deal more to offer in the future.

Psychiatry and the Public. MRS. EDITH M. STERN, Washington, D. C.

A layman would not presume to speak of psychiatrists' relations with patients but would speak only of their relations to the public. Although the relation of psychiatry to the public improved during the war, full popular confidence is still lacking. Advertising and publicity differ from public relations; the latter is concerned with the creation of attitudes. Unfortunately, few psychiatrists are public relations minded. By default, quacks flourish and psychiatrists tend to be consulted only in extreme need, not casually, preventively, as are pediatricians and ophthalmologists. Laymen, even in high places, mistrust psychiatric competence, and journalists tend to misrepresent things psychiatric.

There still exists a medieval hang-over in attitudes toward mental disorders, and psychiatry is viewed as new, vague and untested. However, correction of much popular distrust is within the psychiatrist's control, without sacrifice of professional dignity or integrity. A few suggestions are offered: When writing for laymen, it is advisable to avoid the chance of confusion either with professional polysyllables or with concessions to loose popular terminology. Sensational journalists should not exploit psychoanalysis at the expense of neglecting many other, briefer, more popularly comprehensible technics of psychotherapy. Court decisions evidencing psychologic ignorance, and, above all, press, stage and screen distortions of psychiatry and psychiatrists should be protested.

Public relations are a potent force, and psychiatrists are greatly needed, directly as physicians and indirectly as advisers, in all fields involving human behavior. With this goal in view, the public's confidence must be deliberately cultivated by those concerned.

DISCUSSION

DR. FREDERICK ALLEN: I was privileged to read a brief extract of Mrs. Stern's discussion and felt that the subject was important for this group to have discussed. It is refreshing to get the reactions of lay people. We psychiatrists need to know what others think of us. It is clear that we do have a public responsibility to disseminate in a simple and direct way the knowledge of human nature that we gain from our professional work. We have a responsibility to play a leading role in correcting ignorance and in creating a less prejudiced and more intelligent understanding of mental illness. We should assume leadership in those educational programs designed to help the people in our community to view mental illness with less fear and anxiety. I deliberately say less, rather than no, fear, because we are concerned with an area of professional practice dealing with problems in which the element of fear and anxiety is inherent. There will always be anxiety aroused when persons need to consult a psychiatrist either about themselves or about members of their family. The very nature of the problems for which they need help involves anxiety and fear. When the step is taken with casualness, it frequently has little meaning. It is not human to approach emotional problems without some feeling of fear being aroused. But we can reduce through education and through sound clinical practice the amount of ignorance, the blind prejudice, that still exists about various types of emotional and mental disturbances. This will apply particularly to cases in which it is necessary to place a patient in a hospital for the mentally ill.

We can do a great deal more than we have done to create a more enlightened attitude about the place and function of hospitals for mental disease. Right here in Pennsylvania we are confronted with a very real need of conducting a broad educational program to bring about more adequate support for psychiatric hospitals, in order to assist them to attain higher professional competence and to obtain broader clinical facilities for achieving it. The institutions for the mentally ill are designed to heal, but many of these hospitals today are in no

position adequately to discharge this responsibility. Too frequently they have become custodial places with relatively low professional standards. The staffs of these hospitals are working under terrific handicaps, and they need our able and vigorous support to make them hospitals in fact, and not just in name.

I liked the point Mrs. Stern made concerning the tendency of psychiatrists to become dogmatic in their public utterances. We have all, like Mrs. Stern, heard public statements by psychiatrists that make us squirm. In the field of child psychiatry, the field with which I am most familiar, there has been a strong tendency in public presentation to stress the pathology of parenthood. This has been emphasized so much in the innumerable articles written and speeches made that the impression has been created that parenthood in itself is something of a disease. Emphasis has centered too much on what was wrong with parents and not enough on what they can do, and are doing, to make their relations with children a healthier one. We need to stress more our interest in understanding people as they are and in helping them gain from that basis a feeling of greater self respect and an increased capacity for responsibility. We do not do this merely by pointing out and stressing all the mistakes that parents make. It is this negative emphasis that we need to get away from. Not long ago I heard a psychiatrist, in discussing the effect of fathers being away in military service, state that young boys in this generation are going to grow up to be abnormal because they have not had their fathers. Such statements, it seems to me, are irresponsible and serve only to engender both antagonism toward psychiatry and fear of it.

Mrs. Stern's presentation stresses the responsibility we have toward making psychiatry a more human and dignified professional field. In the long run, that which will do the most toward achieving this end is sound clinical practice in our day to day work with our patients. This in the long run will have much more influence than what we write in magazines or say on the public platform. But if what we say and write can really spread and be based on sound clinical practice, then the lecture and the magazine article become important educational influences.

This more negative emphasis has had an unfortunate application in many recent articles which have stressed the possible abnormalities of returning veterans. Many people were encouraged to feel that the returning soldier was going to return to his community with a curious abnormality and a bundle of complications. This stirred up a great deal of unnecessary and false fear and anxiety. This has not been the psychiatrist's fault only; in fact, many psychiatrists, recognizing this unfortunate tendency, have done a good deal to correct it and to set in motion and bring out a different kind of literature.

Psychiatrists work in a field that seems to lend itself to a great many forms of quackery. Again, this is not the fault of the psychiatrist alone; some of the newspapers and magazines aid and abet this tendency by publishing crazy articles that dramatize something in human nature. As long as there are unbalanced people to write such stuff, it seems possible, unfortunately, for them to find some one willing to publish it. It is not always so easy or so attractive to dramatize the truth. But we need not be too much discouraged, for there probably will continue to be curious samples of psychiatry written about in the press or dramatized in moving pictures. We cannot correct all this, but we can perform our own jobs in such a way that people will gain in time a more enlightened attitude. To contrast attitudes of today with those of ten or twenty years ago can give us courage, for we have come a long way. There is still much to be done, however.

There is just one comment of Mrs. Stern's with which I cannot agree—her reference to getting other professional people to do our work for us, on the basis of our not having time ourselves. This is not a fair description of the important contribution which the social worker has to make in this field. I have never conceived of a social worker simply as a person to whom one can turn over a job; rather, I have felt that the contribution of these workers comes when we work with them on a professional basis. We can learn a great deal from the

trained social worker who has a keen sense of her professional job and of the areas in which she operates.

DR. HOWARD K. PETRY, Harrisburg, Pa.: From the point of view of state hospital work, the psychiatric patient seems almost to be the forgotten man, the friendless man. We psychiatrists have not interested the public in the problem of the mentally ill. Laymen are still afraid of such persons. They still do not want to meet or associate with them. It is still pretty difficult to get even a board of trustees in a psychiatric hospital to go around and see the details of the situation for which they are actually responsible.

In the state hospital system, these conditions arise partly because we have moved inside a fence. We have not lived with the people of the community. We have had our social life within the fence, and one of the hardest things in the average state hospital is to get the staff to become part of the community and to get the community to know them.

In our practical discussions we have not got down to the level of the Anglo-Saxon vocabulary in talking to the people. I think psychiatric institutions have suffered, too, because they have had a bad background. They grew up from the poorhouse and have not been able to escape their ancestry.

I am convinced that as psychiatrists we must sell ourselves to our own profession as an initial step. We must get the psychiatrist into the general hospital and must make the public see that there is no sharp dividing line between mental and physical disease. The younger members of the profession have had better training, but the older ones are still hard to approach on this problem.

DR. ARTHUR P. NOYES, Norristown, Pa.: I don't know that I entirely agree with Mrs. Stern about protesting court decisions. The remedy is probably one of education. Perhaps it would be well if the law schools would send their students for a few weeks to the hospitals for mental diseases, just as the theological schools are beginning to send their students. Nothing has contributed to a better understanding on the part of the clergy with respect to human motivations and mental hygiene than this procedure. If the law students could receive training along the same lines, there would be a much better informed judiciary.

DR. HAROLD PALMER: We have needed to talk over some of these things, and we are grateful to Mrs. Stern for bringing up the subject for discussion. I am tempted to say something in defense of the psychiatrists.

Not long ago a famous agency sent an article submitted to them by an author to several Philadelphia psychiatrists. The latter read the article and pointed out that it was unsound, sensational and inaccurate, but the article was published without a single change. There are a number of such occurrences.

I agree with Dr. Allen that we ought to spend more time on the scare material that has been published on neuropsychiatry during this war. I wonder how many of you saw the bulletin called, "A Thousand a Day," which carried the statement, "A thousand screwballs a day released from the armed services." On the other hand, articles have appeared which counteract these destructive implications. In an article which I have at hand it is stated that of 14,000 veterans who had returned to an industry which employed 130,000 people 29 per cent were neurotic dischargees. Now. in that group the job turn-over was less than the average for the plant. The output of a third of these neuropsychiatric dischargees exceeded the average industrial productivity of the plant, and another third were working at higher skills than they were before they went into the Army.

It may be recalled that 42 per cent of candidates coming up for induction were classified as neuropsychiatric. Some interesting statistical work has been done on the actual percentage of neuropsychiatric cases in the services. When the cases in military service were studied by the same standards as those in civilian life, it was found that the percentage of breakdowns was actually less when the same age groups were compared.

I want to thank Mrs. Stern for throwing light on this matter. We needed it very much.

DR. SAMUEL B. HADDEN: I am sure that many of you were thinking of the words of the immortal bard of Old Scotland:

"Oh wad some power the giftie gie us
To see oursel's as others see us."

We have had this opportunity. The recent meetings conducted by the Philadelphia County Medical Society showed an average attendance of between 400 and 500. People are indeed interested in mental health; and if they do not get information from psychiatrists, they are going to get it from some other source.

The serious problem is with the civilians who did not get into the service. They are by far the more pathetic group, not the returning psychoneurotic soldiers.

We have a contribution to make to better living, and our corrections might well begin in the schools and carry on from first grade, both with the students and with the faculties. The public is interested, and we might as well give them the information, rather than have them get it from some commercial group which will capitalize on it.

DR. A. H. PIERCE: If we are going to sell ourselves to members of the medical profession in general, we have got to do it in as straightforward Anglo-Saxon English as possible. All have heard psychiatrists read papers at medical meetings which only mystified the average practitioner; yet it is perfectly possible to express one's ideas in simple English.

After members of the medical profession have been sold on us in an understanding fashion, it will be easier to reach the public as a whole.

MISS S. O'HARA, Harrisburg, Pa.: I am particularly interested in Mrs. Stern's emphasis on adequate public relations. It happens to be one of my responsibilities as Secretary of the Pennsylvania Department of Welfare, to secure the understanding and the good will not only of the public generally but also of the officialdom of the state. The construction of hospitals alone is not the answer to the problem of mental illness. By that I mean that the public must realize the need for preventive methods. I should like to keep patients out of hospitals for mental disease. Members of the medical and the nursing professions and the public generally must become conscious of the need for diagnostic facilities and preventive psychiatric services in the average-sized community—for care on the part of the general practitioner in the early stages of mental illness.

The need for the services of the psychiatrist is the first which the patient or his family should be conscious of wanting. The need for psychiatric hospitals should follow long after, and I congratulate this society in recognizing the fact and in bringing into this conference a layman like myself to discuss the methods of informing the public.

MRS. EDITH M. STERN, Washington, D. C.: I welcome the improvements which have been made on my suggestions tonight. I think that the idea of more psychiatric writing in popular magazines, instead of in your own journals, is excellent. But it is not a question of writing about the sick mind; the angle should be that of mental health. Also, I believe that it is an excellent idea to have law students go through hospitals for the mentally ill; that is what good public relations mean. My suggestions do not stem from my own opinion of psychiatrists; they represent the unfortunate opinions which I have heard a variety of laymen express.

Psychiatrists must not take the helpless attitude that the press is so terrible, that they cannot do anything about it. They can. It will not be done immediately; but, as I said originally, if psychiatrists do not encourage the reputable writers, the latter will dig their information out of the medical journals. No doubt many unsound writers will still do that. I think that Dr. Palmer's suggestion is fine, to have a public relations committee to establish relations with various writers who can be trusted and to whom psychiatrists can safely give their material.

Government agencies, of course, cannot come right out and refuse to give information to anybody, but they have subtle ways of withholding it from undesirable persons. Psychiatrists can adopt the same policy about giving out or withholding their information.

News and Comment

RESEARCH POSITIONS CREATED

The Honorable S. M. R. O'Hara, Secretary of Welfare of the Commonwealth of Pennsylvania, announces the establishment of twelve positions for research in psychiatry and related fields at the Western State Psychiatric Institute and Clinic, Pittsburgh. At the institute numerous clinical and teaching activities, the latter in collaboration with the University of Pittsburgh School of Medicine, have already been initiated.

The institute is the teaching and research hospital of the Pennsylvania mental hospital system, which includes twenty-one hospitals and institutions, with an average of 40,000 patients. Thus, access to much clinical material is assured. Here, it is expected will be trained psychiatrists, social workers, psychologists, nurses, occupational therapeutists and others for hospitals and private fields.

These new positions provide for the appointment of properly qualified senior and junior research workers in psychiatry, internal medicine, biochemistry, neuropathology, neurophysiology and clinical psychology. Several positions, as in psychology and neurophysiology, are currently filled.

In some instances research at the institute will be coordinated with teaching at the university; in such cases the applicant for appointment, and his qualifications, must meet also with the approval of the dean of the school of medicine.

Interested persons may obtain further information by writing to the director of the institute, Grosvenor B. Pearson, M.D., O'Hara and DeSoto Streets, Pittsburgh 13.

AMERICAN BOARD OF PSYCHIATRY AND NEUROLOGY, INC.

A meeting of the American Board of Psychiatry and Neurology, Inc., will be held in New York, Dec. 16 and 17, 1946. Applications for examination should be completed and in the hands of the secretary by October 6. The December meeting is the last opportunity for the consideration of candidates who desire certification on record.

Dr. F. J. Braceland, 102-110 Second Avenue, S.W., Rochester, Minn., is secretary-treasurer, and the executive offices of the board are at that address.

ASSOCIATION FOR RESEARCH IN NERVOUS AND MENTAL DISEASE

The Association for Research in Nervous and Mental Disease will meet jointly with the International League Against Epilepsy on December 13 and 14 at the Waldorf-Astoria Hotel in New York. The subject for discussion will be Epilepsy. Correspondence may be addressed to Thomas E. Bamford Jr., secretary, Association for Research in Nervous and Mental Disease, 115 East Eighty-Second Street, New York 28.

NINTH ANNUAL LOUIS GROSS MEMORIAL LECTURE

The ninth annual Louis Gross Memorial Lecture will be delivered under the auspices of the Montreal Clinical Society at the Jewish General Hospital, Montreal, on Wednesday, Oct. 23, 1946, at 8:30 p. m., by Dr. Roy R. Grinker, director of the Institute for Psychosomatic and Psychiatric Research and Training of the Michael Reese Hospital, Chicago. The subject will be "Psychiatric Objectives of Our Time."

Book Reviews

Experimental Hypertension. By William Goldring, Richard J. Bing, Eduardo Cruz Coke, W. D. Collings, L. W. Donaldson, M. L. Goldberg, Harry Goldblatt, B. Gomberg, Arthur Grollman, C. A. Johnson, Oliver Kamm, Luis F. Leloir, H. Minatoya, W. G. Moss, Eric Ogden, Irvine H. Page, John W. Remington, L. A. Sapirstein and G. E. Wakerlin. Special Publications of the New York Academy of Sciences, R. W. Miner, Editor, Volume III. Pp. 180. New York, 1946.

The collection of papers gathered into this volume indicates that an understanding of the mechanism of experimental renal hypertension is in the stage of apparently conflicting evidence and opposing views. The papers are those presented in February 1945 at a conference held by the Section of Biology, New York Academy of Sciences, on experimental hypertension and deal for the most part with the so-called renal hypertension experimentally produced. They make little attempt to correlate the evidence but offer the data and opinions of investigators who have explored various phases of the problem.

The renin-angiotonin system—its production and chemistry and the characteristics of its activity—is discussed, but "no conclusive proof [is] offered that it is in fact the cause of . . . elevated blood pressure." Dr. Irvine H. Page presents important support of the humoral pressor theory in demonstrating, on ear vessels of the perfused rabbit, a vasoconstrictor substance differing from angiotonin and present in the blood plasma of animals and man with hypertension. But Grollman, and Ogden and his associates find facts which seemingly cannot be reconciled with the humoral pressor mechanism. Grollman suggests that the operative procedure causes the absence of a substance normally produced by the kidney, and without which hypertension results; Ogden and his co-workers believe that in the production of chronic hypertension a neurogenic mechanism is important.

Whatever the theory, the facts of renal metabolism in hypertension must be explained. Raska (not mentioned in the list of authors) summarizes work on the oxidizing power and concentration of respiratory catalysts in the kidneys in renal hypertension, and Bing shows how the kidney in anaerobic states may produce pressor amines.

The work on renal antipressor extracts is difficult to corrolate, largely because depressor properties are found in various fractions and because different laboratories yield such differing results. "It is generally thought that the effect of these extracts is non-specific." An interesting action of Wakerlin's extract in dogs is the protection of a small number of the animals from experimentally induced hypertension.

In short, the book presents what is known of experimental renal hypertension and indicates the direction of future investigation. The integrating effect of the conference which produced this book seemed much needed.

Motor Disorders in Nervous Diseases. By Ernst Herz, M.D., and Tracy J. Putnam, M.D. Price $3. Pp. 192. New York: Kings Cross Press, 1946.

The development in the use of moving picture films for educational purposes has brought out a treatise appropriately entitled "Motor Disorder in Nervous Diseases," by Drs. Ernst Herz and Tracy J. Putnam.

The work is composed of two parts, an "Atlas" in small textbook form and ten reels. The descriptive atlas, intended for use in conjunction with the films, consists of some 180 pages and is, in a limited sense, a textbook. The work consists solely of an analysis of disturbances of pathologic conditions in the motor sphere. The

book contains elaborate and instructive material, clearly presented, of use both to the student and to the physician. The style, manner and form of presentation are such as to maintain the interest of the reader.

The films are finely executed. The subject matter is profusely illustrated in the book itself by strips from the series of films.

While the text and illustrations are devoted especially to the presentation of purely clinical features of motor disorders, the associated implications of anatomic and pathologic conditions are presented both from an investigative physiologic and from a chemical viewpoint. The relation between motor function and anatomic structure has been considered minutely in the elucidation of the clinical entities and elaborated in the book by means of drawings, both plain and animated.

In developing the various presentations, the authors show the experienced teacher's appreciation of the difficulties of the medical student in passing from the basic studies to his approach to the patient, and both the textbook and the films are an important aid in this part of the student's experience.

The authors have called on experts in special fields of related subjects to aid in elucidation of some of the subjects requiring special explanation, as, for example, in their outline of the physiochemical aspects of neuromuscular transmission, in their discussion of the visual mechanism as related to neurology and in their presentation of neuro-otology.

The following grouping gives an idea of the manner of presentation of the films: The first division deals with "Involuntary Movements in Nervous Diseases." The "Atlas" presents a study of the various types of deformities of movement, including athetosis, dystonic postures, chorea and myoclonus. The book contains excellent descriptions and analyses of these conditions. The film clearly demonstrates the descriptive material. The second film deals with disorders of gait; the third, with disturbances in coordination. One would have to study many textbooks to gather the infomation contained in the few pages on this subject. The fourth film, on muscle status, is an excellent study in disorders resulting from gross and fine pathologic processes of muscle; clinical demonstrations are ample. Of especial interest is discussion on neurophysiologic relations, including the reaction of acetylcholine. The fifth film, on reflexes, deals with clinical demonstrations and pathologic interpretation of the important reflexes. The sixth film, on skilled acts, consists in an analysis of incoordination, akinesia and abnormal involuntary movement, and the various types of motor pattern in eupraxia, apraxia, ideokinetic apraxia (Liepmann) and constructive apraxia (Kleist). In the seventh film, disorders of the ocular system are discussed in detail, with profuse illustrations. The eighth film deals with facial palsy; the ninth, with disorders of the vestibular system. The chapter in the book and the illustrative film constitute a complete study of disorders of the vestibular system; it gives methods of examination with minute elaboration of various tests associated with the pathology of this complicated mechanism. In the tenth film disorders of the motor part of the trigeminal, spinal accessory and hypoglossal nerves are illustrated, with presentation of patients and animated pictures of the anatomy and descriptive pathology.

This valuable contribution to current medical literature should have a wide distribution as a teaching medium. It will find a place in every institution for medical education.